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In this issue:

Heinz Kohut's Self Psychology: An Overview

By Howard S. Baker and Margaret N. Baker

The Discharged Psychiatric Patient:
A Review of Social, Social-Psychological, and Psychiatric
Correlates of Outcome

By William R. Avison and Kathy Nixon Speechley

Official Journal of the American Psychiatric Association



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Contraindications: Comatose or greatly depressed states due to C.N.S. depressants; blood dyscrasias; bone marrow depression; liver damage.

Warnings: Tardive dyskinesia (TD) may develop in patients treated with neuroleptic (antipsychotic) drugs. The risk of TD and likelihood of irreversibility are thought to increase as duration of treatment and total cumulative neuroleptic dose increase. Much less commonly, the syndrome can develop after relatively brief treatment at low doses. There is no known treatment for TD, although it may remit if neuroleptics are withdrawn. Neuroleptic treatment may suppress signs and symptoms of the syndrome and thereby mask the underlying disease process. To minimize risk of TD, generally reserve chronic neuroleptic treatment for patients who suffer from chronic illness that responds to neuroleptics and for whom alternative, effective, less harmful treatments are not available or appropriate. In patients requiring chronic treatment, the minimal effective dose and shortest duration of treatment should be sought. Periodically reassess need for continued treatment. If signs and symptoms of TD appear, discontinuation of neuroleptics should be considered. (See PRECAUTIONS.)

Generally avoid using in patients hypersensitive (e.g., have had blood dyscrasias, jaundice) to any phenothiazine. Caution patients about activities requiring alertness (e.g., operating vehicles or machinery), especially during the first few days' therapy. Additive depressant effect is possible with other C.N.S. depressants, including alcohol. Do not use in pregnancy except when essential and potential benefits clearly outweigh possible hazards. Prolonged jaundice, extrapyramidal signs, hyperreflexia and hyporeflexia have been reported in newborns whose mothers received phenothiazines. There is evidence that phenothiazines are excreted in the breast milk of nursing mothers.

Precautions: Since some patients chronically exposed to neuroleptics will develop tardive dyskinesia, it is advised that, if possible, full information about this risk be given to patients or their guardians when chronic use is contemplated.

Use cautiously in angina. Avoid high doses and parenteral use when cardiovascular system is impaired since hypotension has occurred. Antiemetic effect may mask the signs of

overdosage of other drugs or obscure diagnosis and treatment of certain physical disorders. Prolonged use of high doses may result in cumulative effects with severe C.N.S. or vasomotor symptoms. If retinal changes occur, discontinue drug. Agranulocytosis, thrombocytopenia, pancytopenia, anemia, cholestatic jaundice, liver damage have been reported. Use cautiously in patients with glaucoma.

Patients with a history of long-term therapy with 'Stelazine' and/or other neuroleptics should be evaluated periodically for possible dosage adjustment or discontinuance of drug therapy. Neuroleptic drugs cause elevated prolactin levels that persist during chronic use. Since approximately one-third of human breast cancers are prolactin-dependent *in vitro*, this elevation is of potential importance if neuroleptic drug use is contemplated in a patient with a previously detected breast cancer. However, clinical and epidemiologic studies to date have not shown an association between the chronic use of neuroleptic drugs and mammary tumorigenesis. Use cautiously in persons who will be exposed to extreme heat.

Phenothiazines may diminish the effect of oral anticoagulants. Phenothiazines can produce alpha-adrenergic blockade. Concomitant use of phenothiazines with propranolol increases plasma levels of both drugs. Concurrent use of phenothiazines may counteract antihypertensive effects of guanethidine and related compounds. Thiazide diuretics may accentuate the orthostatic hypotension that may occur with phenothiazines. Phenothiazines may lower the convulsive threshold and may also precipitate phenytoin toxicity; dosage adjustments of anticonvulsants may be necessary. If neuromuscular reactions occur in pregnant women, or in children, permanently stop neuroleptic therapy. Patients should not receive 'Stelazine' 48 hours before or 24 hours after myelography with the contrast medium metrizamide. The presence of phenothiazines may produce false positive phenylketonuria (PKU) test results.

Adverse Reactions: Drowsiness, dizziness, skin reactions, rash, dry mouth, insomnia, amenorrhea, fatigue, muscular weakness, anorexia, lactation, blurred vision. Neuromuscular (extrapyramidal) reactions: motor restlessness, dystonias, pseudo-parkinsonism, tardive dyskinesia, and a variant, tardive dystonia.

Other adverse reactions reported with Stelazine (trifluoperazine HCl, SK&F) or other phenothiazines: Some adverse effects are more frequent or intense in specific disorders (e.g., mitral insufficiency or pheochromocytoma).

Grand mal and petit mal convulsions, particularly in the presence, or with history, of EEG abnormalities; altered cerebrospinal fluid proteins; cerebral edema; prolongation and intensification of the action of C.N.S. depressants, atropine, heat, and organophosphorus insecticides; nasal congestion, headache, nausea, constipation, obstipation, adynamic ileus, ejaculatory disorders/impotence, priapism, atonic colon, urinary retention, miosis and mydriasis; reactivation of psychotic processes, catatonic-like states; hypotension (sometimes fatal); cardiac arrest; leukopenia, eosinophilia, pancytopenia, agranulocytosis, thrombocytopenic purpura, hemolytic anemia, aplastic anemia, jaundice, biliary stasis; hyperglycemia, hypoglycemia, glycosuria, menstrual irregularities, galactorrhea, gynecomastia, false positive pregnancy tests; photosensitivity, itching, erythema, urticaria, eczema up to exfoliative dermatitis; asthma, laryngeal edema, angioneurotic edema, anaphylactoid reactions, peripheral edema; reversed epinephrine effect; hyperpyrexia; mild fever after large I.M. doses; increased appetite; increased weight; a systemic lupus erythematosus-like syndrome; pigmentary retinopathy; with prolonged administration of substantial doses, skin pigmentation, epithelial keratopathy, and lenticular and corneal deposits; neuroleptic malignant syndrome, which may be fatal; EKG changes—particularly nonspecific, usually reversible Q and T wave distortions—have been observed. Temporary nausea, vomiting, dizziness, and tremulousness may follow abrupt cessation of high-dose therapy. NOTE: Sudden death in patients taking phenothiazines (apparently) due to cardiac arrest or asphyxia due to failure of cough reflex) has been reported.

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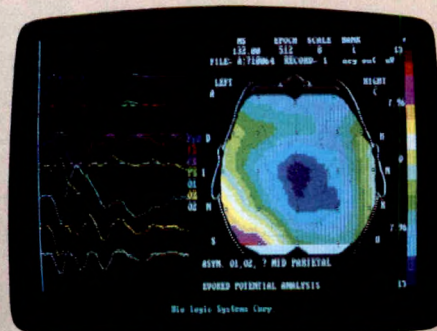
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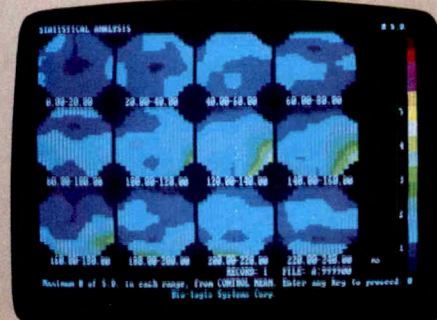
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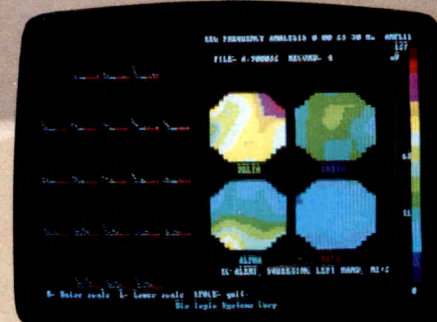
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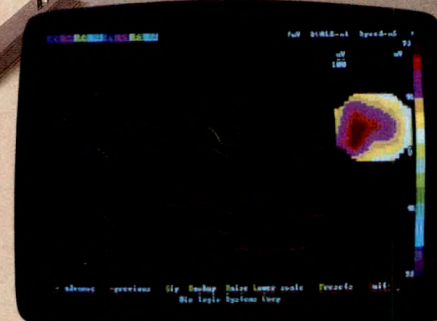
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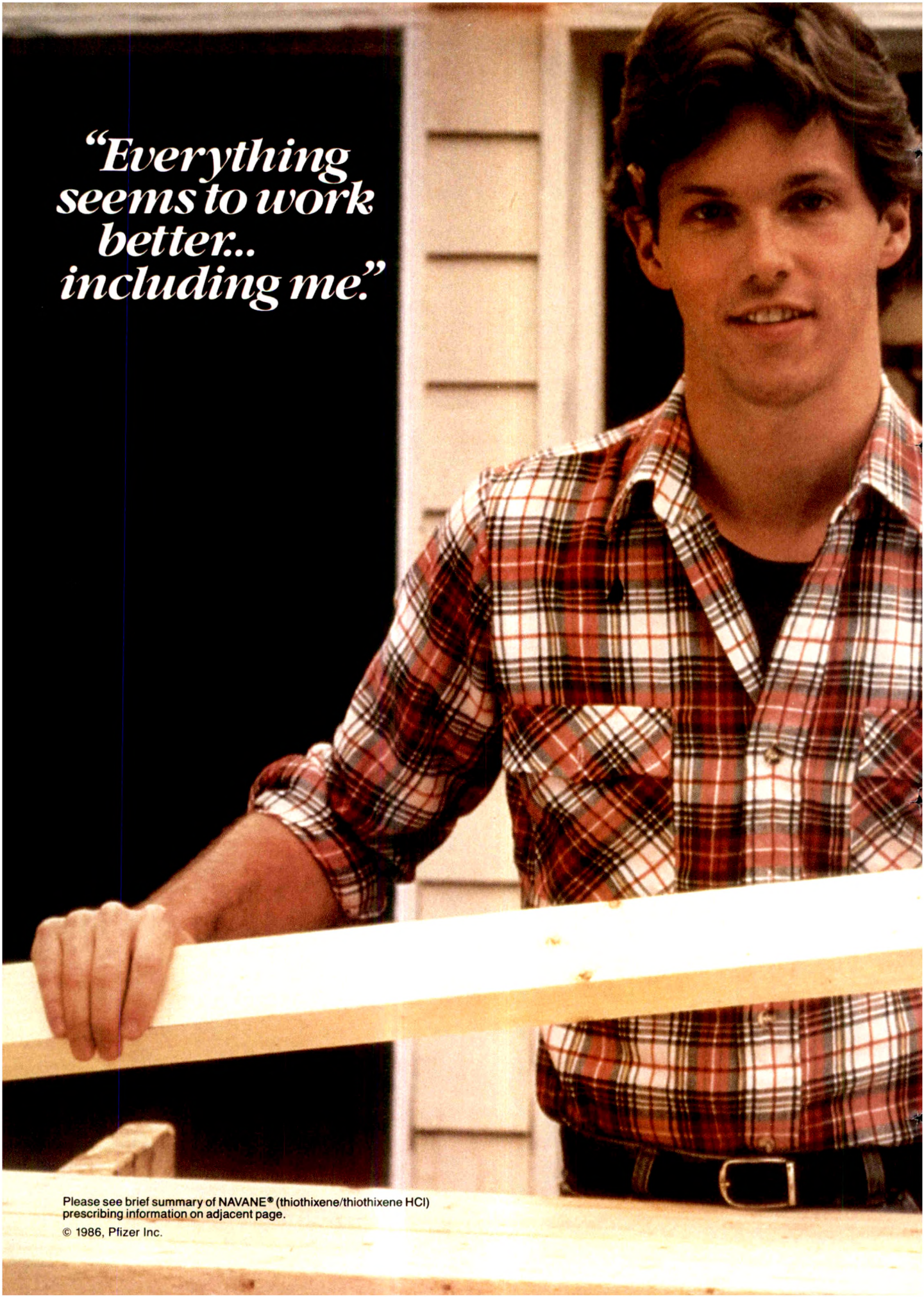
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A color photograph of a young man with dark, wavy hair, smiling slightly. He is wearing a red, white, and black plaid button-down shirt over a dark t-shirt, and a black belt with a silver buckle. He is leaning his right arm on a light-colored wooden railing. The background shows a wooden door or window frame.

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References: 1 Bressler B, Friedel RO: A comparison between chlorpromazine and thiothixene in a Veterans Administration hospital population. *Psychosomatics* 1971;12:275-277. 2 DiMascio A, Demigian E: Study of the activating properties of thiothixene. *Psychosomatics* 1972;13:105-108. 3 DiMascio A, Demigian E: Job training in the rehabilitation of the chronic schizophrenic. Presented at a Scientific Exhibit at The American Psychiatric Association, Washington, DC, May 3-6, 1971. 4 Goldstein B, Weiner D, Banas F: Clinical evaluation of thiothixene in chronic ambulatory schizophrenic patients, in Lehmann HE, Ban TA (eds): *The Thioxanthenes: Modern Problems of Pharmacopsychiatry*. Basel, Switzerland, S Karger, 1969, vol 2, pp 45-52. 5 Dillenkoffler RL, Gallant DM, George RB, et al: Electrocardiographic evaluation of schizophrenic patients: A double-blind comparison. Presented at a Scientific Exhibit at The 125th Annual Meeting of The American Psychiatric Association, Dallas, May 1-4, 1972. 6 Data available on request from Roerig.

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Contraindications: Navane (thiothixene) is contraindicated in patients with circulatory collapse, comatose states, central nervous system depression due to any cause, and blood dyscrasias. Navane is contraindicated in individuals who have shown hypersensitivity to the drug. It is not known whether there is a cross-sensitivity between the thioxanthenes and the phenothiazine derivatives, but the possibility should be considered.

Warnings: *Tardive Dyskinesia*—Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with neuroleptic (antipsychotic) drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of neuroleptic treatment, which patients are likely to develop the syndrome. Whether neuroleptic drug products differ in their potential to cause tardive dyskinesia is unknown.

Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of neuroleptic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if neuroleptic treatment is withdrawn. Neuroleptic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying disease process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, neuroleptics should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic neuroleptic treatment should generally be reserved for patients who suffer from a chronic illness that, 1) is known to respond to neuroleptic drugs, and, 2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on neuroleptics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome.

(For further information about the description of tardive dyskinesia and its clinical detection, please refer to the section on Adverse Reactions.)

Usage in Pregnancy—Safe use of Navane during pregnancy has not been established. Therefore, this drug should be given to pregnant patients only when, in the judgment of the physician, the expected benefits from the treatment exceed the possible risks to mother and fetus. Animal reproduction studies and clinical experience to date have not demonstrated any teratogenic effects.

In the animal reproduction studies with Navane, there was some decrease in conception rate and litter size, and an increase in resorption rate in rats and rabbits, changes which have been similarly reported with other psychotropic agents. After repeated oral administration of Navane to rats (5 to 15 mg/kg/day), rabbits (3 to 50 mg/kg/day), and monkeys (1 to 3 mg/kg/day) before and during gestation, no teratogenic effects were seen. (See Precautions.)

Usage in Children—The use of Navane in children under 12 years of age is not recommended because safety and efficacy in the pediatric age group have not been established.

As is true with many CNS drugs, Navane may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery, especially during the first few days of therapy. Therefore, the patient should be cautioned accordingly.

As in the case of other CNS-acting drugs, patients receiving Navane should be cautioned about the possible additive effects (which may include hypotension) with CNS depressants and with alcohol.

Precautions: An antiemetic effect was observed in animal studies with Navane; since this effect may also occur in man, it is possible that Navane may mask signs of overdosage of toxic drugs and may obscure conditions such as intestinal obstruction and brain tumor.

In consideration of the known capability of Navane and certain other psychotropic drugs to precipitate convulsions, extreme caution should be used in patients with a history of convulsive disorders or those in a state of alcohol withdrawal since it may lower the convulsive threshold. Although Navane potentiates the actions of the barbiturates, the dosage of the anticonvulsant therapy should not be reduced when Navane is administered concurrently.

Caution as well as careful adjustment of the dosage is indicated when Navane is used in conjunction with other CNS depressants other than anticonvulsant drugs.

Though exhibiting rather weak anticholinergic properties, Navane should be used with caution in patients who are known or suspected to have glaucoma, or who might be exposed to extreme heat, or who are receiving atropine or related drugs.

Use with caution in patients with cardiovascular disease.

Also, careful observation should be made for pigmentary retinopathy, and lenticular pigmentation (fine lenticular pigmentation has been noted in a small number of patients treated with Navane for prolonged periods). Blood dyscrasias (agranulocytosis, pancytopenia, thrombocytopenic purpura), and liver damage (jaundice, biliary stasis) have been reported with related drugs.

Undue exposure to sunlight should be avoided. Photosensitive reactions have been reported in patients on Navane.

Neuroleptic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of neuroleptic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time.

Intramuscular Administration—As with all intramuscular preparations, Navane Intramuscular should be injected well within the body of a relatively large muscle. The preferred sites are the upper outer quadrant of the buttock (i.e. gluteus maximus) and the mid-lateral thigh.

The deltoid area should be used only if well developed, such as in certain adults and older children, and then only with caution to avoid radial nerve injury. Intramuscular injections should not be made into the lower and mid-thirds of the upper arm. As with all intramuscular injections, aspiration is necessary to help avoid inadvertent injection into a blood vessel.

Adverse Reactions: *Note:* Not all of the following adverse reactions have been reported with Navane (thiothixene). However, since Navane has certain chemical and pharmacologic similarities to the phenothiazines, all of the known side effects and toxicity associated with phenothiazine therapy should be borne in mind when Navane is used.

Cardiovascular effects: Tachycardia, hypotension, lightheadedness, and syncope. In the event hypotension occurs, epinephrine should not be used as a pressor agent since a paradoxical further lowering of blood pressure may result. Nonspecific EKG changes have been observed in some patients receiving Navane (thiothixene). These changes are usually reversible and frequently disappear on continued Navane therapy. The incidence of these changes is lower than that observed with some phenothiazines. The clinical significance of these changes is not known.

CNS effects: Drowsiness, usually mild, may occur although it usually subsides with continuation of Navane therapy. The incidence of sedation appears similar to that of the piperazine group of phenothiazines, but less than that of certain aliphatic phenothiazines. Restlessness, agitation and insomnia have been noted with Navane. Seizures and paradoxical exacerbation of psychotic symptoms have occurred with Navane infrequently.

Hyperreflexia has been reported in infants delivered from mothers having received structurally related drugs. In addition, phenothiazine derivatives have been associated with cerebral edema and cerebrospinal fluid abnormalities.

Extrapyramidal symptoms, such as pseudo-parkinsonism, akathisia, and dystonia have been reported. Management of these extrapyramidal symptoms depends upon the type and severity. Rapid relief of acute symptoms may require the use of an injectable antiparkinson agent. More slowly emerging symptoms may be managed by reducing the dosage of Navane and/or administering an oral antiparkinson agent.

Persistent Tardive Dyskinesia: As with all antipsychotic agents tardive dyskinesia may appear in some patients on long term therapy or may occur after drug therapy has been discontinued. The risk seems to be greater in elderly patients on high-dose therapy, especially females. The symptoms are persistent and in some patients appear to be irreversible. The syndrome is characterized by rhythmic involuntary movements of the tongue, face, mouth or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities.

Since early detection of tardive dyskinesia is important, patients should be monitored on an ongoing basis. It has been reported that fine vermicular movement of the tongue may be an early sign of the syndrome. If this or any other presentation of the syndrome is observed, the clinician should consider possible discontinuation of neuroleptic medication. (See Warnings section.)

Hepatic Effects: Elevations of serum transaminase and alkaline phosphatase, usually transient, have been infrequently observed in some patients. No clinically confirmed cases of jaundice attributable to Navane have been reported.

Hematologic Effects: As is true with certain other psychotropic drugs, leukopenia and leukocytosis, which are usually transient, can occur occasionally with Navane. Other antipsychotic drugs have been associated with agranulocytosis, eosinophilia, hemolytic anemia, thrombocytopenia and pancytopenia.

Allergic Reactions: Rash, pruritus, urticaria, photosensitivity and rare cases of anaphylaxis have been reported with Navane. Undue exposure to sunlight should be avoided. Although not experienced with Navane, exfoliative dermatitis and contact dermatitis (in nursing personnel) have been reported with certain phenothiazines.

Endocrine Disorders: Lactation, moderate breast enlargement and amenorrhea have occurred in a small percentage of females receiving Navane. If persistent, this may necessitate a reduction in dosage or the discontinuation of therapy. Phenothiazines have been associated with false positive pregnancy tests, gynecomastia, hypoglycemia, hyperglycemia, and glycosuria.

Autonomic Effects: Dry mouth, blurred vision, nasal congestion, constipation, increased sweating, increased salivation, and impotence have occurred infrequently with Navane therapy. Phenothiazines have been associated with miosis, mydriasis, and adynamic ileus.

Other Adverse Reactions: Hyperpyrexia, anorexia, nausea, vomiting, diarrhea, increase in appetite and weight, weakness or fatigue, polydipsia and peripheral edema.

Although not reported with Navane, evidence indicates there is a relationship between phenothiazine therapy and the occurrence of a systemic lupus erythematosus-like syndrome.

NOTE: Sudden deaths have occasionally been reported in patients who have received certain phenothiazine derivatives. In some cases the cause of death was apparently cardiac arrest or asphyxia due to failure of the cough reflex. In others, the cause could not be determined nor could it be established that death was due to phenothiazine administration.

Dosage and Administration: Dosage of Navane should be individually adjusted depending on the chronicity and severity of the condition. In general, small doses should be used initially and gradually increased to the optimal effective level, based on patient response.

Some patients have been successfully maintained on once-a-day Navane therapy.

Usage in children under 12 years of age is not recommended because safe conditions for its use have not been established.

Navane Intramuscular Solution: Navane For Injection—When more rapid control and treatment of acute behavior is desirable, the intramuscular form of Navane may be indicated. It is also of benefit where the very nature of the patient's symptomatology, whether acute or chronic, renders oral administration impractical or even impossible.

For treatment of acute symptomatology or in patients unable or unwilling to take oral medication, the usual dose is 4 mg of Navane Intramuscular administered 2 to 4 times daily. Dosage may be increased or decreased depending on response. Most patients are controlled on a total daily dosage of 16 to 20 mg. The maximum recommended dosage is 30 mg/day. An oral form should supplant the injectable form as soon as possible. It may be necessary to adjust the dosage when changing from the intramuscular to oral dosage forms. Dosage recommendations for Navane (thiothixene) Capsules and Concentrate appear in the following paragraphs.

Navane Capsules: Navane Concentrate—In milder conditions, an initial dose of 2 mg three times daily. If indicated, a subsequent increase to 15 mg/day total daily dose is often effective.

In more severe conditions, an initial dose of 5 mg twice daily.

The usual optimal dose is 20 to 30 mg daily. If indicated, an increase to 60 mg/day total daily dose is often effective. Exceeding a total daily dose of 60 mg rarely increases the beneficial response.

Overdosage: Manifestations include muscular twitching, drowsiness, and dizziness. Symptoms of gross overdosage may include CNS depression, rigidity, weakness, torticollis, tremor, salivation, dysphagia, hypotension, disturbances of gait, or coma.

Treatment: Essentially is symptomatic and supportive. For Navane oral, early gastric lavage is helpful. For Navane oral and Intramuscular, keep patient under careful observation and maintain an open airway, since involvement of the extrapyramidal system may produce dysphagia and respiratory difficulty in severe overdosage. If hypotension occurs, the standard measures for managing circulatory shock should be used (i.e. fluids and/or vasoconstrictors.)

If a vasoconstrictor is needed, levarterenol and phenylephrine are the most suitable drugs. Other pressor agents, including epinephrine, are not recommended, since phenothiazine derivatives may reverse the usual pressor action of these agents and cause further lowering of the blood pressure.

If CNS depression is present and specific therapy is indicated, recommended stimulants include amphetamine, dextroamphetamine, or caffeine and sodium benzoate. Stimulants that may cause convulsions (e.g. picrotoxin or pentylenetetrazol) should be avoided. Extrapyramidal symptoms may be treated with antiparkinson drugs.

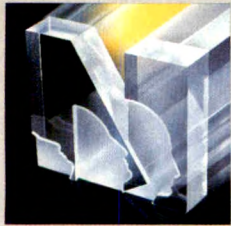
There are no data on the use of peritoneal or hemodialysis, but they are known to be of little value in phenothiazine intoxication.

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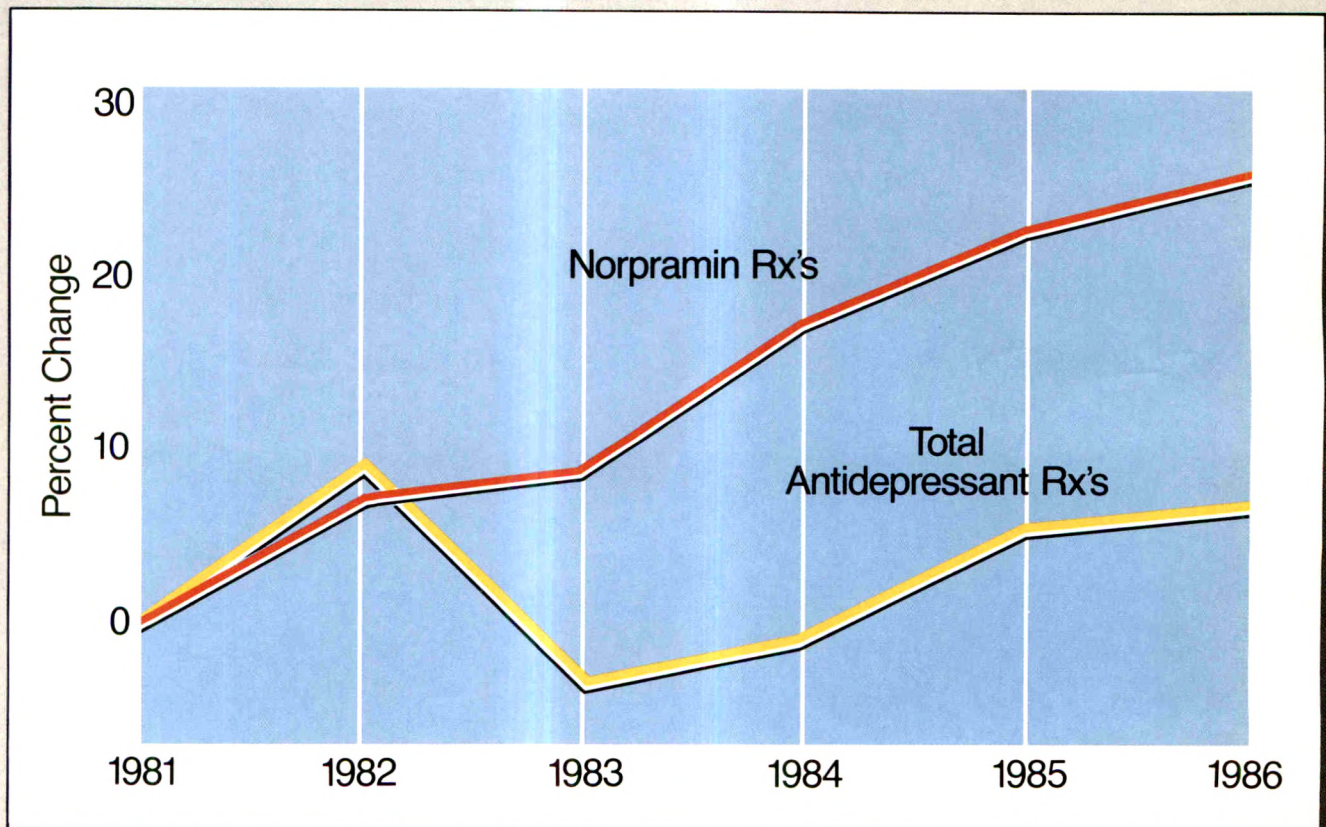


Figure 1.







The red line tracks the percent change in Norpramin prescriptions; the yellow line represents the percent change in total prescription activity for the antidepressant market (based on IMS International *National Prescription Audit*, June 1986).

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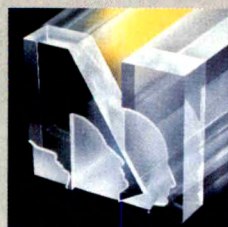
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- the choice of a once or twice daily single tablet dosage, and the added flexibility of six different dosage strengths

1. Greenberg RN: Overview of patient compliance with medication dosing: A literature review. Clin Ther 6:592-599, 1984.
Brief Summary of Prescribing Information appears on the next page.



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Convenient choice of six tablet strengths and once daily or divided dosage schedule allows titration to individual response.



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Norpramin®

(desipramine hydrochloride tablets USP)

AVAILABLE ONLY ON PRESCRIPTION

Brief Summary

MECHANISM OF ACTION: Available evidence suggests that many depressions have a biochemical basis in the form of a relative deficiency of neurotransmitters such as norepinephrine and serotonin. Norepinephrine deficiency may be associated with relatively low urinary 3-methoxy-4-hydroxyphenyl glycol (MHPG) levels, while serotonin deficiencies may be associated with low spinal fluid levels of 5-hydroxyindolacetic acid.

While the precise mechanism of action of the tricyclic antidepressants is unknown, a leading theory suggests that they restore normal levels of neurotransmitters by blocking the re-uptake of these substances from the synapse in the central nervous system.

Evidence indicates that the secondary amine tricyclic antidepressants, including Norpramin, may have greater activity in blocking the re-uptake of norepinephrine. Tertiary amine tricyclic antidepressants, such as amitriptyline, may have greater effect on serotonin re-uptake.

Norpramin (desipramine hydrochloride) is not a monoamine oxidase (MAO) inhibitor and does not act primarily as a central nervous system stimulant. It has been found in some studies to have a more rapid onset of action than imipramine. Earliest therapeutic effects may occasionally be seen in 2 to 5 days, but full treatment benefit usually requires 2 to 3 weeks to obtain.

INDICATIONS: Norpramin (desipramine hydrochloride) is indicated for relief of symptoms in various depressive syndromes, especially endogenous depression.

CONTRAINDICATIONS: Desipramine hydrochloride should not be given in conjunction with, or within 2 weeks of, treatment with an MAO inhibitor drug; hyperpyretic crises, severe convulsions, and death have occurred in patients taking MAO inhibitors and tricyclic antidepressants. When Norpramin (desipramine hydrochloride) is substituted for an MAO inhibitor, at least 2 weeks should elapse between treatments. Norpramin should then be started cautiously and should be increased gradually.

The drug is contraindicated in the acute recovery period following myocardial infarction. It should not be used in those who have shown prior hypersensitivity to the drug. Cross sensitivity between this and other dibenzazepines is a possibility.

WARNINGS: 1. Extreme caution should be used when this drug is given in the following situations: a. In patients with cardiovascular disease, because of the possibility of conduction defects, arrhythmias, tachycardias, strokes, and acute myocardial infarction. b. In patients with a history of urinary retention or glaucoma, because of the anticholinergic properties of the drug. c. In patients with thyroid disease or those taking thyroid medication, because of the possibility of cardiovascular toxicity, including arrhythmias. d. In patients with a history of seizure disorder, because this drug has been shown to lower the seizure threshold. 2. This drug is capable of blocking the antihypertensive effect of guanethidine and similarly acting compounds. 3. **USE IN PREGNANCY:** Safe use of desipramine hydrochloride during pregnancy and lactation has not been established; therefore, if it is to be given to pregnant patients, nursing mothers, or women of child-bearing potential, the possible benefits must be weighed against the possible hazards to mother and child. Animal reproductive studies have been inconclusive. 4. **USE IN CHILDREN:** Norpramin (desipramine hydrochloride) is not recommended for use in children since safety and effectiveness in the pediatric age group have not been established. 5. The patient should be cautioned that this drug may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. 6. In patients who may use alcohol excessively, it should be borne in mind that the potentiation may increase the danger inherent in any suicide attempt or overdose.

PRECAUTIONS: 1. It is important that this drug be dispensed in the least possible quantities to depressed outpatients, since sui-

cide has been accomplished with this class of drug. Ordinary prudence requires that children not have access to this drug or to potent drugs of any kind; if possible, this drug should be dispensed in containers with child-resistant safety closures. Storage of this drug in the home must be supervised responsibly. 2. If serious adverse effects occur, dosage should be reduced or treatment should be altered. 3. Norpramin (desipramine hydrochloride) therapy in patients with manic-depressive illness may induce a hypomanic state after the depressive phase terminates.

4. The drug may cause exacerbation of psychosis in schizophrenic patients. 5. Close supervision and careful adjustment of dosage are required when this drug is given concomitantly with anticholinergic or sympathomimetic drugs. 6. Patients should be warned that while taking this drug their response to alcoholic beverages may be exaggerated. 7. Clinical experience in the concurrent administration of ECT and antidepressant drugs is limited. Thus, if such treatment is essential, the possibility of increased risk relative to benefits should be considered. 8. If Norpramin (desipramine hydrochloride) is to be combined with other psychotropic agents such as tranquilizers or sedative-hypnotics, careful consideration should be given to the pharmacology of the agents employed since the sedative effects of Norpramin and benzodiazepines (e.g., chlordiazepoxide or diazepam) are additive. Both the sedative and anticholinergic effects of the major tranquilizers are also additive to those of Norpramin. 9. This drug should be discontinued as soon as possible prior to elective surgery because of the possible cardiovascular effects. Hypertensive episodes have been observed during surgery in patients taking desipramine hydrochloride. 10. Both elevation and lowering of blood sugar levels have been reported. 11. Leukocyte and differential counts should be performed in any patient who develops fever and sore throat during therapy; the drug should be discontinued if there is evidence of pathologic neutrophil depression. 12. Norpramin 25, 50, 75, and 100 mg tablets contain FD&C Yellow No. 5 (tartrazine), which may cause allergic-type reactions (including bronchial asthma) in certain susceptible individuals. Although the overall incidence of FD&C Yellow No. 5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity.

ADVERSE REACTIONS: Note: Included in the following listing are a few adverse reactions that have not been reported with this specific drug. However, the pharmacologic similarities among the tricyclic antidepressant drugs require that each of the reactions be considered when Norpramin (desipramine hydrochloride) is given.

Cardiovascular: hypotension, hypertension, tachycardia, palpitation, arrhythmias, heart block, myocardial infarction, stroke.

Psychiatric: confusional states (especially in the elderly) with hallucinations, disorientation, delusions, anxiety, restlessness, agitation; insomnia and nightmares; hypomania; exacerbation of psychosis.

Neurologic: numbness, tingling, paresthesias of extremities; incoordination, ataxia, tremors; peripheral neuropathy; extrapyramidal symptoms; seizures; alteration in EEG patterns; tinnitus.

Anticholinergic: dry mouth, and rarely associated sublingual adenitis; blurred vision, disturbance of accommodation, mydriasis, increased intraocular pressure; constipation, paralytic ileus; urinary retention, delayed micturition, dilatation of urinary tract.

Allergic: skin rash, petechiae, urticaria, itching, photosensitization (avoid excessive exposure to sunlight), edema (of face and tongue or general), drug fever, cross sensitivity with other tricyclic drugs.

Hematologic: bone marrow depressions including agranulocytosis, eosinophilia, purpura, thrombocytopenia.

Gastrointestinal: anorexia, nausea and vomiting, epigastric distress, peculiar taste, abdominal cramps, diarrhea, stomatitis, black tongue.

Endocrine: gynecomastia in the male, breast enlargement and galactorrhea in the female; increased or decreased libido, impotence, testicular swelling; elevation or depression of blood sugar levels.

Other: jaundice (simulating obstructive), altered liver function; weight gain or loss; perspiration, flushing; urinary frequency, nocturia; parotid swelling; drowsiness, dizziness, weakness and fatigue, headache; alopecia.

Withdrawal Symptoms: Though not indicative of addiction, abrupt cessation of treatment after prolonged therapy may produce nausea, headache, and malaise.

DOSAGE AND ADMINISTRATION: Not recommended for use in children. Lower dosages are recommended for elderly patients and adolescents. Lower dosages are also recommended for outpatients compared to hospitalized patients, who are closely supervised. Dosage should be initiated at a low level and increased according to clinical response and any evidence of intolerance. Following remission, maintenance medication may be required for a period of time and should be at the lowest dose that will maintain remission.

Usual Adult Dose: The usual adult dose is 100 to 200 mg per day. In more severely ill patients, dosage may be further increased gradually to 300 mg/day if necessary. Dosages above 300 mg/day are not recommended.

Dosage should be initiated at a lower level and increased according to tolerance and clinical response.

Treatment of patients requiring as much as 300 mg should generally be initiated in hospitals, where regular visits by the physician, skilled nursing care, and frequent electrocardiograms (ECG's) are available.

The best available evidence of impending toxicity from very high doses of Norpramin is prolongation of the QRS or QT intervals on the ECG. Prolongation of the PR interval is also significant, but less closely correlated with plasma levels. Clinical symptoms of intolerance, especially drowsiness, dizziness, and postural hypotension, should also alert the physician to the need for reduction in dosage. Plasma desipramine measurement would constitute the optimal guide to dosage monitoring.

Initial therapy may be administered in divided doses or a single daily dose.

Maintenance therapy may be given on a once-daily schedule for patient convenience and compliance.

Adolescent and Geriatric Dose: The usual adolescent and geriatric dose is 25 to 100 mg daily.

Dosage should be initiated at a lower level and increased according to tolerance and clinical response to a usual maximum of 100 mg daily. In more severely ill patients, dosage may be further increased to 150 mg/day. Doses above 150 mg/day are not recommended in these age groups.

Initial therapy may be administered in divided doses or a single daily dose.

Maintenance therapy may be given on a once-daily schedule for patient convenience and compliance.

OVERDOSAGE: See prescribing information for a discussion of symptoms and treatment of overdose.

Product Information as of January, 1985.

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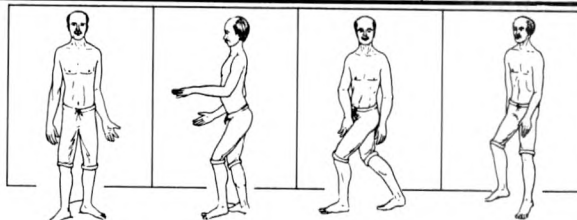
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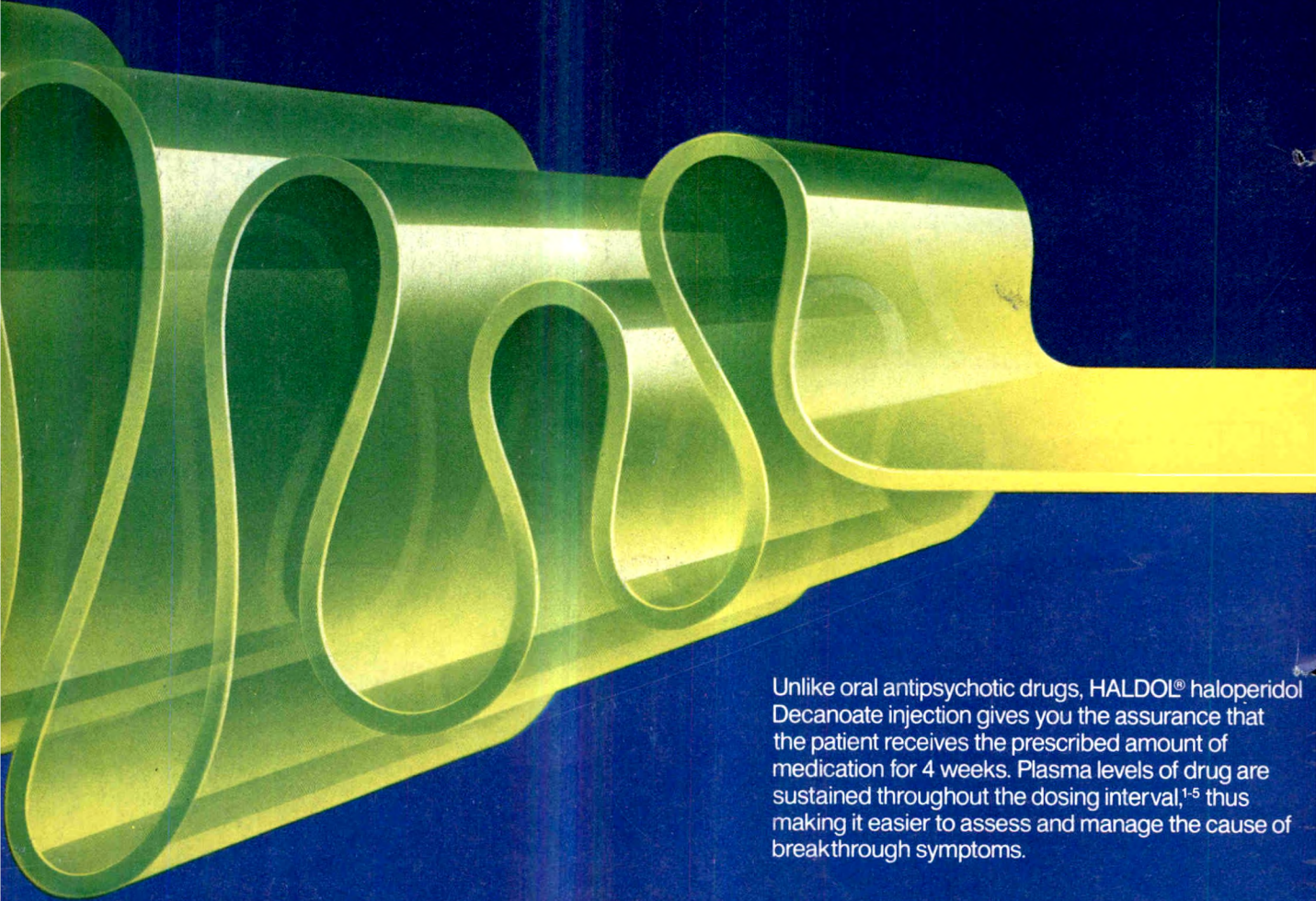
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An abstract graphic featuring a thick, green, wavy ribbon-like structure that flows from the left side of the frame towards the right. The ribbon has several large, rounded loops and undulations, giving it a sense of movement and fluidity. The color of the ribbon transitions from a deep green on the left to a bright yellow-green on the right. The background is a solid, dark blue with a subtle vertical texture.

Unlike oral antipsychotic drugs, HALDOL® haloperidol Decanoate injection gives you the assurance that the patient receives the prescribed amount of medication for 4 weeks. Plasma levels of drug are sustained throughout the dosing interval,¹⁻⁵ thus making it easier to assess and manage the cause of breakthrough symptoms.

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The side effects of HALDOL Decanoate are those of HALDOL. The prolonged action of HALDOL Decanoate should be considered in the management of side effects. During dose adjustment or episodes of exacerbation of psychotic symptoms, HALDOL Decanoate therapy can be supplemented with short-acting forms of HALDOL. It is recommended that patients being considered for HALDOL Decanoate therapy be initially converted to oral HALDOL (from whatever other neuroleptic they are taking) in order to exclude the possibility of an unexpected adverse sensitivity to haloperidol. HALDOL Decanoate is administered only by deep intramuscular injection.

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References

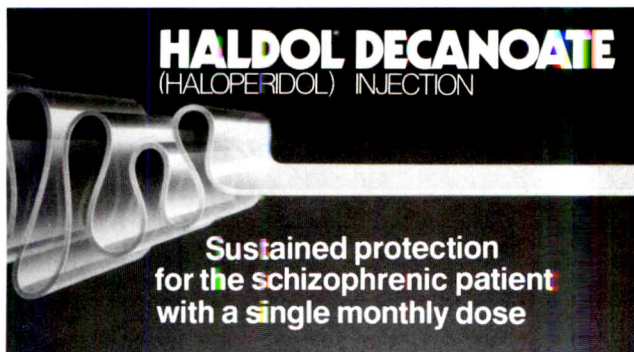
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Please see brief summary of prescribing information on next page.



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PHARMACEUTICAL**
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The following is a brief summary only. Before prescribing, see complete prescribing information in HALDOL Decanoate product labeling.

Contraindications: Since the pharmacologic and clinical actions of HALDOL (haloperidol) Decanoate are attributed to HALDOL as the active medication, contraindications, warnings, and additional information are those of HALDOL, modified only to reflect the prolonged action.

HALDOL is contraindicated in severe toxic central nervous system depression or comatose states from any cause and in individuals who are hypersensitive to this drug or have Parkinson's disease.

Warnings: *Tardive Dyskinesia*—A syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with neuroleptic (antipsychotic) drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of neuroleptic treatment, which patients are likely to develop the syndrome. Whether neuroleptic drug products differ in their potential to cause tardive dyskinesia is unknown.

Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of neuroleptic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if neuroleptic treatment is withdrawn. Neuroleptic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, neuroleptics should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic neuroleptic treatment should generally be reserved for patients who suffer from a chronic illness that 1) is known to respond to neuroleptic drugs, and 2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on neuroleptics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome. (For further information about the description of tardive dyskinesia and its clinical detection, please refer to ADVERSE REACTIONS.)

General—A number of cases of bronchopneumonia, some fatal, have followed the use of major tranquilizers, including HALDOL (haloperidol). It has been postulated that lethargy and decreased sensation of thirst due to central inhibition may lead to dehydration, hemoconcentration and reduced pulmonary ventilation. Therefore, if the above signs and symptoms appear, especially in the elderly, the physician should institute remedial therapy promptly.

Although not reported with HALDOL, decreased serum cholesterol and/or cutaneous and ocular changes have been reported in patients receiving chemically-related drugs.

Precautions: HALDOL (haloperidol) Decanoate should be administered cautiously to patients:

- with severe cardiovascular disorders, because of the possibility of transient hypotension and/or precipitation of anginal pain. Should hypotension occur and a vasopressor be required, epinephrine should not be used since HALDOL may block its vasopressor activity and paradoxical further lowering of the blood pressure may occur.
- receiving anticonvulsant medications, with a history of seizures, or with EEG abnormalities, because HALDOL may lower the convulsive threshold. If indicated, adequate anticonvulsant therapy should be concomitantly maintained.
- with known allergies, or with a history of allergic reactions to drugs.
- receiving anticoagulants, since an isolated instance of interference occurred with the effects of one anticoagulant (phenindione).

If concomitant antiparkinson medication is required, it may have to be continued after HALDOL Decanoate is discontinued because of the prolonged action of HALDOL Decanoate. If both drugs are discontinued simultaneously, extrapyramidal symptoms may occur. The physician should keep in mind the possible increase in intraocular pressure when anticholinergic drugs, including antiparkinson agents, are administered concomitantly with HALDOL Decanoate. In patients with thyrotoxicosis who are also receiving antipsychotic medication, including HALDOL Decanoate, severe neurotoxicity (rigidity, inability to walk or talk) may occur.

When HALDOL is used to control mania in bipolar disorders, there may be a rapid mood swing to depression.

Information for Patients: HALDOL Decanoate may impair the mental and/or physical abilities required for the performance of hazardous tasks such as operating machinery or driving a motor vehicle. The ambulatory patient should be warned accordingly.

The use of alcohol with this drug should be avoided due to possible additive effects and hypotension.

Drug Interactions: An encephalopathic syndrome (characterized by weakness, lethargy, fever, tremor, drowsiness and confusion, extrapyramidal symptoms, leukocytosis, elevated serum enzymes, BUN, and FBS) followed by irreversible brain damage has occurred in a few patients treated with lithium plus HALDOL. A causal relationship between these events and the concomitant administration of lithium and HALDOL has not been established; however, patients receiving such combined therapy should be monitored closely for early evidence of neurological toxicity and treatment discontinued promptly if such signs appear.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: No mutagenic potential of haloperidol decanoate was found in the Ames Salmonella microsome activation assay.

Carcinogenicity studies using oral haloperidol were conducted in Wistar rats (dosed at up to 5 mg/kg daily for 24 months) and in Albino Swiss mice (dosed at up to 5 mg/kg daily for 18 months). In the rat study survival was less than optimal in all dose groups, reducing the number of rats at risk for developing tumors. However, although a relatively greater number of rats survived to the end of the study in high dose male and female groups, these animals did not have a greater incidence of tumors than control animals. Therefore, although not optimal, this study does suggest the absence of a haloperidol-related increase in the incidence of neoplasia in rats at doses up to 20 times the usual daily human dose for chronic or resistant patients.

In female mice at 5 and 20 times the highest initial daily dose for chronic or resistant patients, there was a statistically significant increase in mammary gland neoplasia and total tumor incidence; at 20 times the same daily dose there was a statistically significant increase in pituitary gland neoplasia. In male mice, no statistically significant differences in incidences of total tumors or specific tumor types were noted.

Neuroleptic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent in vivo, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of neuroleptic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time.

Usage in Pregnancy: Pregnancy Category C. Rodents given up to 3 times the usual maximum human dose of

haloperidol decanoate showed an increase in incidence of resorption, fetal mortality, and pup mortality. No fetal abnormalities were observed.

Cleft palate has been observed in mice given oral haloperidol at 15 times the usual maximum human dose. Cleft palate in mice appears to be a non-specific response to stress or nutritional imbalance as well as to a variety of drugs, and there is no evidence to relate this phenomenon to predictable human risk for most of these agents.

There are no adequate and well-controlled studies in pregnant women. There are reports, however, of cases of limb malformations observed following maternal use of HALDOL along with other drugs which have suspected teratogenic potential during the first trimester of pregnancy. Causal relationships were not established with these cases. Since such experience does not exclude the possibility of fetal damage due to HALDOL, HALDOL Decanoate should be used during pregnancy or in women likely to become pregnant only if the benefit clearly justifies a potential risk to the fetus.

Nursing Mothers: Since haloperidol is excreted in human breast milk, infants should not be nursed during drug treatment with HALDOL Decanoate.

Pediatric Use: Safety and effectiveness of HALDOL Decanoate in children have not been established.

Adverse Reactions: Adverse reactions following the administration of HALDOL (haloperidol) Decanoate are those of HALDOL. Since vast experience has accumulated with HALDOL, the adverse reactions are reported for that compound as well as for HALDOL Decanoate. As with all injectable medications, local tissue reactions have been reported with HALDOL Decanoate.

CNS Effects: *Extrapyramidal Reactions*—Neuromuscular (extrapyramidal) reactions during the administration of HALDOL have been reported frequently, often during the first few days of treatment. These have also been reported with HALDOL Decanoate. In most patients, these reactions involved Parkinson-like symptoms which, when first observed, were usually mild to moderately severe and usually reversible. Other types of neuromuscular reactions (motor restlessness, dystonia and tardive dyskinesia, akathisia, hyperreflexia, opisthotonos, oculogyric crises) have been reported far less frequently, but were often more severe. Severe extrapyramidal reactions have been reported to occur at relatively low doses. Generally the occurrence and severity of most extrapyramidal symptoms are dose-related since they occur at relatively high doses and have been shown to disappear or become less severe when the dose is reduced. Administration of antiparkinson drugs such as benztropine mesylate U.S.P. or trihexyphenidyl hydrochloride U.S.P. may be required for control of such reactions. It should be noted that persistent extrapyramidal reactions have been reported and that the drug may have to be discontinued in such cases.

Withdrawal Emergent Neurological Signs—Generally, patients receiving short term therapy experience no problems with abrupt discontinuation of antipsychotic drugs. However, some patients on maintenance treatment experience transient dyskinetic signs after abrupt withdrawal. In certain of these cases the dyskinetic movements are indistinguishable from the syndrome described below under "Tardive Dyskinesia" except for duration. Although the long acting properties of HALDOL Decanoate provide gradual withdrawal, it is not known whether gradual withdrawal of antipsychotic drugs will reduce the rate of occurrence of withdrawal emergent neurological signs.

Tardive Dyskinesia—As with all antipsychotic agents HALDOL has been associated with persistent dyskinesias. Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may appear in some patients on long-term therapy with HALDOL Decanoate or may occur after drug therapy has been discontinued. The risk appears to be greater in elderly patients on high-dose therapy, especially females. The symptoms are persistent and in some patients appear irreversible. The syndrome is characterized by rhythmic involuntary movements of tongue, face, mouth, or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities.

There is no known effective treatment for tardive dyskinesia; antiparkinson agents usually do not alleviate the symptoms of this syndrome. It is suggested that all antipsychotic agents be discontinued if these symptoms appear. Should it be necessary to reinstitute treatment, or increase the dosage of the agent, or switch to a different antipsychotic agent, this syndrome may be masked.

It has been reported that fine vermicular movement of the tongue may be an early sign of the syndrome and if the medication is stopped at that time the syndrome may not develop.

Other CNS effects—Insomnia, restlessness, anxiety, euphoria, agitation, drowsiness, depression, lethargy, headache, confusion, vertigo, grand mal seizures, exacerbation of psychotic symptoms including hallucinations, and catatonic-like behavioral states which may be responsive to drug withdrawal and/or treatment with anticholinergic drugs.

Body as a Whole: As with other neuroleptic drugs, a symptom complex sometimes referred to as neuroleptic malignant syndrome (NMS) has been reported. Cardinal features of NMS are hyperpyrexia, muscle rigidity, altered mental status (including catatonic signs), and evidence of autonomic instability (irregular pulse or blood pressure). Additional signs may include elevated CPK, myoglobinuria (rhabdomyolysis), and acute renal failure. NMS is potentially fatal, requires intensive symptomatic treatment and discontinuation of neuroleptic treatment.

Hypertoxia and heat stroke, not associated with the above symptom complex, have also been reported with HALDOL.

Cardiovascular Effects: Tachycardia, hypotension, hypertension and ECG changes.

Hematologic Effects: Reports have appeared citing the occurrence of mild and usually transient leukopenia and leukocytosis, minimal decreases in red blood cell counts, anemia, or a tendency toward lymphomonocytosis. Agranulocytosis has rarely been reported to have occurred with the use of HALDOL, and then only in association with other medication.

Liver Effects: Impaired liver function and/or jaundice have been reported.

Dermatologic Reactions: Maculopapular and acneiform skin reactions and isolated cases of photosensitivity and loss of hair.

Endocrine Disorders: Lactation, breast engorgement, mastalgia, menstrual irregularities, gynecostasia, impotence, increased libido, hyperglycemia, hypoglycemia and hyponatremia.

Gastrointestinal Effects: Anorexia, constipation, diarrhea, hypersalivation, dyspepsia, nausea and vomiting.

Ophthalmic Reactions: Dry mouth, blurred vision, urinary retention and diaphoresis.

Respiratory Effects: Laryngospasm, bronchospasm and increased depth of respiration.

Special Senses: Cataracts, retinopathy and visual disturbances.

Other: Cases of sudden and unexpected death have been reported in association with the administration of HALDOL. The nature of the evidence makes it impossible to determine definitively what role, if any, HALDOL played in the outcome of the reported cases. The possibility that HALDOL caused death cannot, of course, be excluded, but it is to be kept in mind that sudden and unexpected death may occur in psychotic patients when they go untreated or when they are treated with other neuroleptic drugs.

Dosage and Administration: HALDOL (haloperidol) Decanoate should be administered by deep intramuscular injection into the gluteal region. A 2" long 21 gauge needle is recommended. The maximum volume per injection site should not exceed 3 mL. The recommended interval between doses is 4 weeks. DO NOT ADMINISTER INTRAVENOUSLY.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

HALDOL Decanoate is intended for use in chronic psychotic patients who require prolonged parenteral neuroleptic therapy. These patients should be previously stabilized on antipsychotic medication before considering a conversion to HALDOL Decanoate. Furthermore, it is recommended that patients being considered for HALDOL Decanoate therapy be initially converted to oral haloperidol (from whatever other neuroleptic they are taking) in order to exclude the possibility of an unexpected adverse sensitivity to haloperidol. Close clinical supervision is required during the initial period of dose adjustment in order to minimize the risk of overdosage or reappearance of psychotic symptoms before the next injection. During dose adjustment or episodes of exacerbation of psychotic symptoms, HALDOL Decanoate therapy can be supplemented with short-acting forms of haloperidol.

The starting dose of HALDOL Decanoate should be based on the patient's clinical history, physical condition, and response to previous antipsychotic therapy. The preferred approach to determining the minimum effective dose is to begin with lower initial doses and to adjust the dose upward as needed. It is recommended that the initial dose of HALDOL Decanoate be 10-15 times the previous daily dose in oral haloperidol equivalents, but no more than a maximum initial dose of 100 mg (2 mL). HALDOL Decanoate has been effectively administered at monthly intervals in several clinical studies. However, variation in patient response may dictate a need for adjustment of the dosing interval as well as the dose.

Lower initial doses and more gradual adjustment are recommended for elderly or debilitated patients.

Clinical experience with HALDOL Decanoate at doses greater than 300 mg (6 mL) per month has been limited.

Full instructions for use should be read before administering or prescribing.

For information on symptoms and treatment of overdosage, see full prescribing information.

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Calendar

For free listing of your organization's official annual or regional meeting, please send us the following information: sponsor, location, inclusive dates, type and number of continuing education credits (if available), and the name, address, and telephone number of the person or group to contact for more information. All notices and changes must be received no later than 120 days before the first day of the month of desired publication and should be addressed to Calendar, American Journal of Psychiatry, 1400 K St., N.W., Washington, DC 20005. Because of space limitations, only listings of meetings of the greatest interest to Journal readers will be included.

MARCH

March 4-7, annual meeting, Association for Academic Psychiatry, Tampa, Fla. Contact Mary O'Loughlin, Admin. Asst., Dept. of Psychiatry, Mount Auburn Hospital, Cambridge, MA 02238; 617-499-5008.

March 6-10, 5th World Congress of the World Association for Dynamic Psychiatry, Munich, Germany, F.R. Contact Lehr- und Forschungsinstitut für Dynamische Psychiatrie und Gruppendynamik Wielandstr. 27/28, 1000 Berlin 15, Germany F.R.; 030-88-18059.

March 7, 10th Annual Alcohol Symposium, Diagnosis & Treatment: New Perspectives on Old Dilemmas, Boston. Contact Judy Reiner Platt, Ed.D., Cambridge Hospital, 1493 Cambridge St., Cambridge, MA 02139; 617-864-6165.

March 13, The 1987 Revision of the Psychiatric Diagnostic and Statistical Manual: Implications for Practice, University of Minnesota, Minneapolis. Contact Office of Continuing Medical Education, Box 202 UMHC, 420 Delaware St., S.E., Minneapolis, MN 55455; 612-626-5525.

March 18-22, annual meeting, American Medical Student Association, New Orleans. Contact Paul R. Wright, Executive Director, 1910 Association Dr., Reston, VA 22091; 703-620-6600.

March 19-20, semiannual meeting, American Board of Medical Specialties, Chicago. Contact Donald G. Langsley, M.D., Executive Vice-President, 1 American Plaza, Suite 805, Evanston, IL 60201; 312-491-9091.

March 19-22, annual meeting, Society of Behavioral Medicine, Washington, D.C. Contact Judith C. Woodward, Executive Director, P.O. Box 8530, University Station, Knoxville, TN 37996; 615-974-5164.

March 20-25, International Symposium on Psychiatry, University of Illinois and the Simon Bolivar Program, Bogota, Colombia. Contact Luis Vasquez, M.D., MILA, 38760 Northwoods Dr., Wadsworth, IL 60083; 312-249-1900.

March 25-29, annual meeting, American Orthopsychiatric Association, Washington, D.C. Contact ORTHO, 19 W. 44th St., Suite 1616, New York, NY 10036; 212-354-5770.

March 26-27, 3rd National Traumatic Brain Injury Symposium, Maryland Institute for Emergency Medical Services Systems, Baltimore. Contact Roberta Schwartz, M.Ed.,

CCC-SLP, MIEMSS, 22 S. Greene St., Baltimore, MD 21201; 301-528-6101.

March 26-27, 34th National Health Forum, San Diego. Contact National Health Council, Inc., 622 Third Ave., 34th Fl., New York, NY 10017-6765; 212-972-2700.

March 26-29, annual meeting, American Psychosomatic Society, Philadelphia. Contact Joan K. Erpf, Executive Assistant, 265 Nassau Rd., Roosevelt, NY 11575; 516-379-0191.

March 28, 15th Annual Pratt Creative Arts Therapy Expo, Brooklyn, N.Y. Contact Pratt Creative Arts Therapy Dept., Pratt Institute, Brooklyn, NY 11205; 718-636-3428.

March 29-April 1, annual meeting, National Council on the Aging, Inc., Chicago. Contact Jack Ossofsky, Executive Director, 600 Maryland Ave., S.W., West Wing 100, Washington, DC 20024; 202-479-1200.

APRIL

April 1-5, The Future of Adult Life: 1st International Conference, the Netherlands. Contact Conference Secretariat, c/o CONGREX, Keizersgracht 610, 1017 EP Amsterdam, the Netherlands; 3120-270401; Telex 14527 CONGRX.

April 2-5, annual meeting, American College of Physicians, New Orleans. Contact John Ball, M.D., Executive Vice-President, 4200 Pine St., Philadelphia, PA 19104; 215-243-1200.

April 5-8, annual meeting, American Occupational Therapy Association, Indianapolis. Contact James J. Garibaldi, Executive Director, 1383 Piccard Dr., Suite 300, Rockville, MD 20850; 301-948-9626.

April 5-9, International Conference on New Directions in Affective Disorders, Jerusalem. Contact Conference Secretariat, International Ltd., New Directions in Affective Disorders, 12 Shlomzion Hamalka St., Jerusalem 94 146 Israel.

April 5-11, annual meeting, American Academy of Neurology, New York. Contact Jan W. Kolehmainen, Executive Director, 2221 University Ave., S.E., Suite 335, Minneapolis, MN 55414; 612-623-8115.

April 6-11, annual meeting, American Society of Clinical Hypnosis, Las Vegas. Contact William F. Hoffmann, Jr.,

(Continued on page A48)

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Contraindications: Known hypersensitivity to the drug.

Warnings: Warn patients that mental and/or physical abilities required for tasks such as driving or operating machinery may be impaired, as may be mental alertness in children, and that concomitant use with alcohol or CNS depressants may have an additive effect. Though physical and psychological dependence have rarely been reported on recommended doses, use caution in administering to addiction-prone individuals or those who might increase dosage. Withdrawal symptoms (including convulsions) reported after abrupt cessation of extended use of excessive doses are similar to those seen with barbiturates. Milder symptoms reported infrequently when continuous therapy is abruptly ended. Avoid abrupt discontinuation; gradually taper dosage.

Usage in Pregnancy: Use of minor tranquilizers during the first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.

Precautions: In the elderly and debilitated, and in children over six, limit to smallest effective dosage (initially 10 mg or less per day) to preclude ataxia or oversedation, increasing gradually as needed and tolerated. Not recommended in children under six. Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider individual pharmacologic effects, particularly in use of potentiating drugs such as MAO inhibitors and phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions (e.g., excitement, stimulation and acute rage) have been reported in psychiatric patients and hyperactive aggressive children. Employ usual precautions in treatment of anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation have been reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship has not been established clinically. Due to isolated reports of exacerbation, use with caution in patients with porphyria.

Adverse Reactions: Drowsiness, ataxia and confusion may occur, especially in the elderly and debilitated. These are reversible in most instances by proper dosage adjustment, but are also occasionally observed at the lower dosage ranges. In a few instances syncope has been reported. Also encountered are isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent and generally controlled with dosage reduction; changes in EEG patterns (low-voltage fast activity) may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice and hepatic dysfunction have been reported occasionally, making periodic blood counts and liver function tests advisable during protracted therapy.

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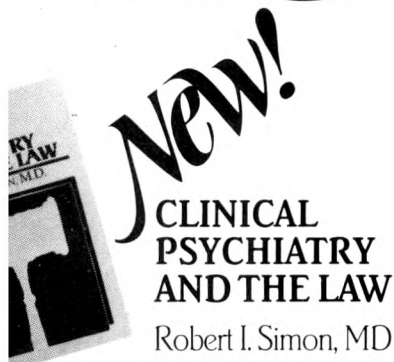
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CONTRAINDICATIONS: In the presence of suspected or established subcortical brain damage. In patients who have a blood dyscrasia or liver damage, or who are receiving large doses of hypnotics, or who are comatose or severely depressed. In patients who have shown hypersensitivity to fluphenazine; cross-sensitivity to phenothiazine derivatives may occur. Fluphenazine Decanoate is not intended for use in children under 12.

WARNINGS: **Tardive Dyskinesia**—potentially irreversible, involuntary, dyskinetic movements may develop. This syndrome appears to be most prevalent among the elderly, especially women; however, prevalence estimates do not reliably predict, at the inception of neuroleptic treatment, those patients likely to develop the syndrome. It is unknown if neuroleptics differ in their potential to cause tardive dyskinesia. The risk of developing the syndrome and the likelihood of its irreversibility are believed to increase as duration of treatment and cumulative dose increase. Although uncommon, the syndrome can develop after brief treatment at low doses. There is no known treatment for tardive dyskinesia, although partial or complete remission may occur with withdrawal of the neuroleptic. Neuroleptic treatment may suppress signs and symptoms of the syndrome and may mask the underlying disease process. The effect of symptomatic suppression on the long-term course of the syndrome is unknown. Neuroleptics should, thus, be prescribed with consideration for the potential of tardive dyskinesia. Chronic treatment should generally be reserved for patients with chronic illness that responds to neuroleptic drugs, and for whom alternative effective, less harmful treatments are not available or appropriate. Patients requiring chronic treatment should receive the smallest dose and shortest duration of treatment producing a satisfactory clinical response. Continuation of treatment should be reassessed periodically. If signs and symptoms of tardive dyskinesia appear, neuroleptic discontinuation should be considered. However, some patients may require continued treatment. (See PRECAUTIONS AND ADVERSE REACTIONS.)

Mental and physical abilities required for driving a car or operating heavy machinery may be impaired by use of this drug. Potentiation of effects of alcohol may occur. Safety and efficacy in children have not been established because of inadequate experience in use in children. Severe adverse reactions, requiring immediate medical attention, may possibly occur.

Usage In Pregnancy: Safety for use during pregnancy has not been established; weigh possible hazards against potential benefits if administering any of these drugs to pregnant patients.

PRECAUTIONS: Caution must be exercised if another phenothiazine compound caused cholestatic jaundice, dermatoses or other allergic reactions because of the possibility of cross-sensitivity. Prolixin Tablets (Fluphenazine Hydrochloride Tablets USP) 2.5, 5, and 10 mg contain FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible individuals. Although the overall incidence of FD&C Yellow No. 5 (tartrazine) sen-

sitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity. When psychotic patients on large doses of a phenothiazine drug are to undergo surgery, hypotensive phenomena should be watched for; less anesthetics or central nervous system depressants may be required. Because of added anticholinergic effects, fluphenazine may potentiate the effects of atropine.

Use fluphenazine cautiously in patients exposed to extreme heat or phosphorus insecticides; in patients with a history of convulsive disorders, since grand mal convulsions have occurred; and in patients with special medical disorders, such as mitral insufficiency or other cardiovascular diseases and pheochromocytoma. Bear in mind that with prolonged therapy there is the possibility of liver damage, pigmentary retinopathy, lenticular and corneal deposits, and development of irreversible dyskinesia.

Neuroleptic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of neuroleptic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time.

Periodic checking of hepatic and renal functions and blood picture should be done. Monitor renal function of patients on long-term therapy; if BUN becomes abnormal, discontinue fluphenazine. "Silent pneumonias" are possible. Fluphenazine decanoate should be administered under the direction of a physician experienced in the clinical use of psychotropic drugs.

Information for Patients: It is likely that some patients exposed chronically to neuroleptics will develop tardive dyskinesia; full information should be given to all patients, if possible, who are candidates for chronic use. Informing patients and/or guardians must take into account clinical circumstances and patient competency.

Abrupt Withdrawal: In general, phenothiazines do not produce psychic dependence. However, gastritis, nausea and vomiting, dizziness, and tremulousness have been reported following abrupt cessation of high dose therapy; reports suggest that these symptoms can be reduced if concomitant antiparkinsonian agents are continued for several weeks after the phenothiazine is withdrawn.

ADVERSE REACTIONS: **Central Nervous System:** Extrapyramidal symptoms are most frequently reported. Most often these symptoms are reversible, but they may be persistent. They include pseudoparkinsonism, dystonia, dyskinesia, akathisia, oculogyric crises, opisthotonos, and hyperreflexia. Muscle rigidity sometimes accompanied by hyperthermia has been reported following use of fluphenazine decanoate. One can expect a higher incidence of such reactions with fluphenazine decanoate than with less potent piperazine derivatives or straight-chain phenothiazines. The incidence and severity of such reactions will depend more on individual patient sensitivity, but dosage level and patient age are also determinants. As these reactions may be alarming, the patient should be forewarned and reassured. These reactions can usually be controlled by administration of an antiparkinsonian drug such as benztropine mesylate and by subsequent reduction in dosage.

Tardive Dyskinesia: See WARNINGS. Characterized by involuntary choreo-athetoid movements involving tongue, face, mouth, lips, or jaw (e.g., tongue protrusion, puffing cheeks, puckering mouth, chewing movements), trunk and extremities. Severity and degree of impairment vary widely. May become clinically recognizable either during treatment, dosage reduction, or treatment withdrawal. To facilitate early detection, reduce dosage periodically (if clinically possible) and observe for signs of the disorder, especially since neuroleptics may mask the signs of the syndrome.

References: 1. Baldessarini RJ: Drugs and the treatment of psychiatric disorders, in Gilman AG, Goodman LS (eds): The Pharmacological Basis of Therapeutics, ed 6. New York, Macmillan Publishing Co, Inc., 1980, p 415. 2. Mason AS, Granacher RP: Clinical Handbook of Antipsychotic Drug Therapy. New York, Brunner/Mazel, 1980, pp 203, 221, 239.

Rare occurrences of neuroleptic malignant syndrome (NMS) have been reported in patients on neuroleptic therapy. The syndrome is characterized by hyperthermia, muscular rigidity, autonomic instability (labile blood pressure, tachycardia, diaphoresis), akinesia, and altered consciousness, sometimes progressing to stupor or coma. Leukocytosis, elevated CPK, liver function abnormalities, and acute renal failure may also occur. Neuroleptic therapy should be discontinued immediately and vigorous symptomatic treatment implemented since the syndrome is potentially fatal.

Phenothiazine derivatives have been known to cause restlessness, excitement, or bizarre dreams; reactivation or aggravation of psychotic processes may be encountered. If drowsiness or lethargy occurs, the dosage may need to be reduced. Dosages, far in excess of the recommended amounts, may induce a catatonic-like state.

Autonomic Nervous System: Hypertension and fluctuations in blood pressure have been reported. Although hypotension is rarely a problem, patients with pheochromocytoma, cerebral vascular or renal insufficiency, or a severe cardiac reserve deficiency such as mitral insufficiency appear to be particularly prone to this reaction and should be observed carefully. Supportive measures including intravenous vasopressor drugs should be instituted immediately should severe hypotension occur. Levarterenol Bitartrate Injection is the most suitable drug; *epinephrine should not be used* since phenothiazine derivatives have been found to reverse its action. Nausea, loss of appetite, salivation, polyuria, perspiration, dry mouth, headache, and constipation may occur. Reducing or temporarily discontinuing the dosage will usually control these effects. Blurred vision, glaucoma, bladder paralysis, fecal impaction, paralytic ileus, tachycardia, or nasal congestion have occurred in some patients on phenothiazine derivatives.

Metabolic and Endocrine: Weight change, peripheral edema, abnormal lactation, gynecocystitis, menstrual irregularities, false results on pregnancy tests, impotency in men and increased libido in women have occurred in some patients on phenothiazine therapy.

Allergic Reactions: Itching, erythema, urticaria, seborrhea, photosensitivity, eczema and exfoliative dermatitis have been reported with phenothiazines. The possibility of anaphylactoid reactions should be borne in mind.

Hematologic: Blood dyscrasias including leukopenia, agranulocytosis, thrombocytopenic or nonthrombocytopenic purpura, eosinophilia, and pancytopenia have been observed with phenothiazines. If soreness of the mouth, gums or throat, or any symptoms of upper respiratory infection occur and confirmatory leukocyte count indicates cellular depression, therapy should be discontinued and other appropriate measures instituted immediately.

Hepatic: Liver damage manifested by cholestatic jaundice, particularly during the first months of therapy, may occur; treatment should be discontinued. A cephalin flocculation increase, sometimes accompanied by alterations in other liver function tests, has been reported in patients who have had no clinical evidence of liver damage.

Others: Sudden deaths have been reported in hospitalized patients on phenothiazines. Previous brain damage or seizures may be predisposing factors. High doses should be avoided in known seizure patients. Shortly before death, several patients showed flare-ups of psychotic behavior patterns. Autopsy findings have usually revealed acute fulminating pneumonia or pneumonitis, aspiration of gastric contents, or intramyocardial lesions. Although not a general feature of fluphenazine, potentiation of central nervous system depressants such as opiates, analgesics, antihistamines, barbiturates and alcohol may occur.

Systemic lupus erythematosus-like syndrome, hypotension severe enough to cause fatal cardiac arrest, altered electrocardiographic and electroencephalographic tracings, altered cerebrospinal fluid proteins, cerebral edema, asthma, laryngeal edema, and angioneurotic edema; with long-term use, skin pigmentation, and lenticular and corneal opacities have occurred with phenothiazines. Local tissue reactions occur only rarely with injections of fluphenazine decanoate.

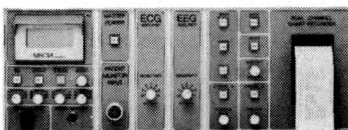
HOW SUPPLIED: Tablets—1 mg, 2.5 mg, 5 mg, and 10 mg in bottles of 50, 100 and 500, and in Unimatic® cartons of 100. Elixir—in bottles of 473 mL (1 pint) and in 60 mL dropper-assembly bottles with calibrated dropper. Oral Concentrate—in bottles of 120 mL with calibrated dropper. Injection—in multiple-dose vials of 10 mL. Fluphenazine Decanoate—in 1 mL Unimatic® single dose preassembled syringes and 5 mL vials.

For full prescribing information, consult package inserts. (J4-120/147/153/150)

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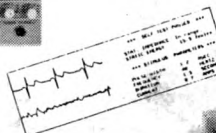
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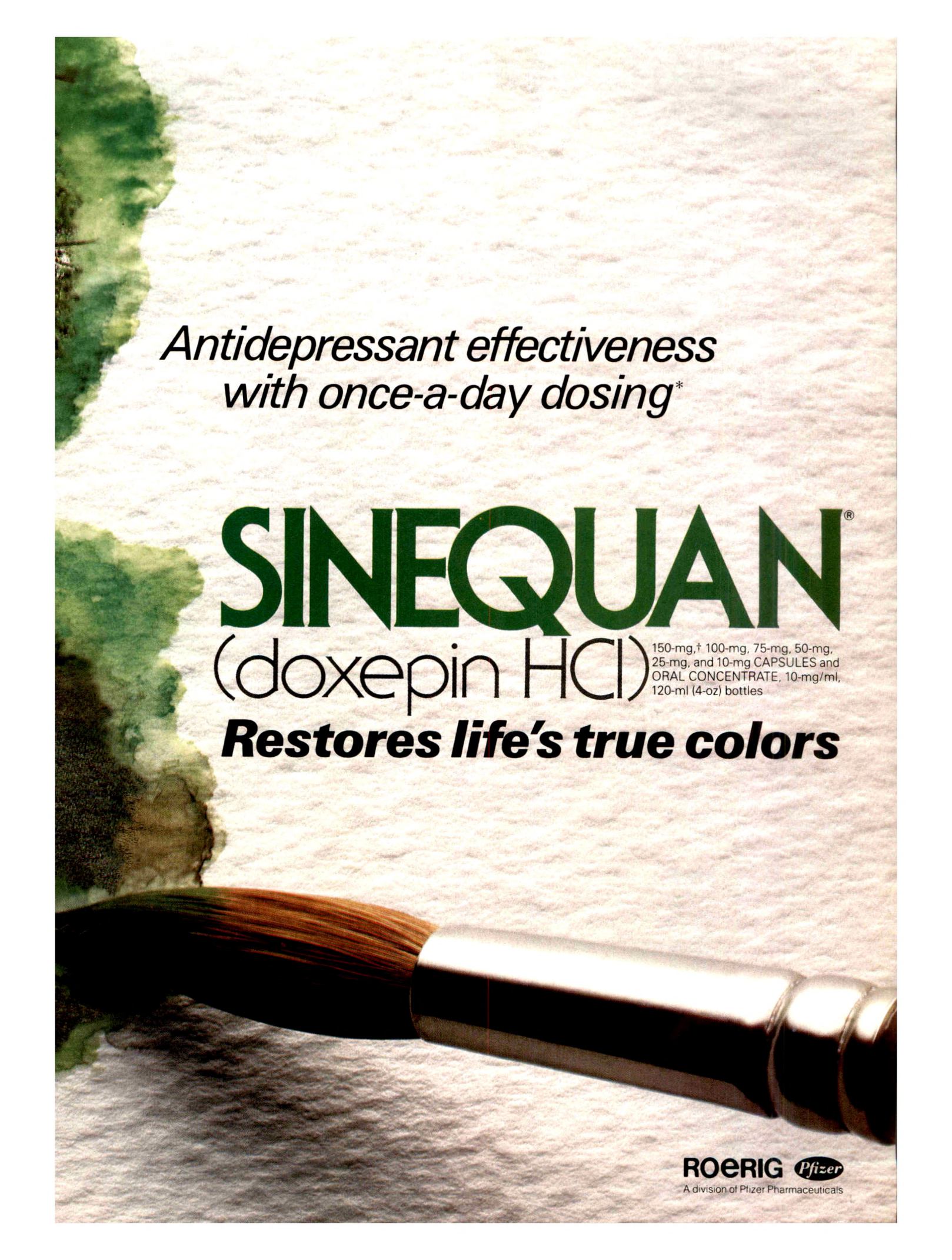


*The total daily dosage of Sinequan may be given on a divided or once-a-day dosage schedule. If the once-a-day schedule is employed, the maximum recommended dose is 150 mg. This dose may be given at bedtime.

†The 150-mg capsule strength is intended for maintenance therapy only and is not recommended for initiation of treatment.

For a brief summary of SINEQUAN prescribing information including adverse reactions, please see the following page of this advertisement.

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*Antidepressant effectiveness
with once-a-day dosing**

SINEQUAN[®]
(doxepin HCl)

150-mg,† 100-mg, 75-mg, 50-mg,
25-mg, and 10-mg CAPSULES and
ORAL CONCENTRATE, 10-mg/ml,
120-ml (4-oz) bottles

Restores life's true colors

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A division of Pfizer Pharmaceuticals

SINEQUAN® (doxepin HCl)

BRIEF SUMMARY

SINEQUAN® (doxepin HCl) Capsules/Oral Concentrate

Contraindications. SINEQUAN is contraindicated in individuals who have shown hypersensitivity to the drug. Possibility of cross sensitivity with other dibenzoxepines should be kept in mind.

SINEQUAN is contraindicated in patients with glaucoma or a tendency to urinary retention. These disorders should be ruled out, particularly in older patients.

Warnings. The once-a-day dosage regimen of SINEQUAN in patients with intercurrent illness or patients taking other medications should be carefully adjusted. This is especially important in patients receiving other medications with anticholinergic effects.

Usage in Geriatrics: The use of SINEQUAN on a once-a-day dosage regimen in geriatric patients should be adjusted carefully based on the patient's condition.

Usage in Pregnancy: Reproduction studies have been performed in rats, rabbits, monkeys and dogs and there was no evidence of harm to the animal fetus. The relevance to humans is not known. Since there is no experience in pregnant women who have received this drug, safety in pregnancy has not been established. There are no data with respect to the secretion of the drug in human milk and its effect on the nursing infant.

Usage in Children: The use of SINEQUAN in children under 12 years of age is not recommended because safe conditions for its use have not been established.

MAO Inhibitors: Serious side effects and even death have been reported following the concomitant use of certain drugs with MAO inhibitors. Therefore, MAO inhibitors should be discontinued at least two weeks prior to the cautious initiation of therapy with SINEQUAN. The exact length of time may vary and is dependent upon the particular MAO inhibitor being used, the length of time it has been administered, and the dosage involved.

Usage with Alcohol: It should be borne in mind that alcohol ingestion may increase the danger inherent in any intentional or unintentional SINEQUAN overdose. This is especially important in patients who may use alcohol excessively.

Precautions. Since drowsiness may occur with the use of this drug, patients should be warned of the possibility and cautioned against driving a car or operating dangerous machinery while taking the drug. Patients should also be cautioned that their response to alcohol may be potentiated.

Since suicide is an inherent risk in any depressed patient and may remain so until significant improvement has occurred, patients should be closely supervised during the early course of therapy. Prescriptions should be written for the smallest feasible amount.

Should increased symptoms of psychosis or shift to manic symptomatology occur, it may be necessary to reduce dosage or add a major tranquilizer to the dosage regimen.

Adverse Reactions. NOTE: Some of the adverse reactions noted below have not been specifically reported with SINEQUAN use. However, due to the close pharmacological similarities among the tricyclics, the reactions should be considered when prescribing SINEQUAN.

Anticholinergic Effects: Dry mouth, blurred vision, constipation, and urinary retention have been reported. If they do not subside with continued therapy, or become severe, it may be necessary to reduce the dosage.

Central Nervous System Effects: Drowsiness is the most commonly noticed side effect. This tends to disappear as therapy is continued. Other infrequently reported CNS side effects are confusion, disorientation, hallucinations, numbness, paresthesias, ataxia, and extrapyramidal symptoms and seizures.

Cardiovascular: Cardiovascular effects including hypotension and tachycardia have been reported occasionally.

Allergic: Skin rash, edema, photosensitization, and pruritus have occasionally occurred.

Hematologic: Eosinophilia has been reported in a few patients. There have been occasional reports of bone marrow depression manifesting as agranulocytosis, leukopenia, thrombocytopenia, and purpura.

Gastrointestinal: Nausea, vomiting, indigestion, taste disturbances, diarrhea, anorexia, and aphthous stomatitis have been reported. (See anticholinergic effects.)

Endocrine: Raised or lowered libido, testicular swelling, gynecomastia in males, enlargement of breasts and galactorrhea in the female, raising or lowering of blood sugar levels, and syndrome of inappropriate antidiuretic hormone have been reported with tricyclic administration.

Other: Dizziness, tinnitus, weight gain, sweating, chills, fatigue, weakness, flushing, jaundice, alopecia, and headache have been occasionally observed as adverse effects.

Withdrawal Symptoms: The possibility of development of withdrawal symptoms upon abrupt cessation of treatment after prolonged SINEQUAN administration should be borne in mind. These are not indicative of addiction and gradual withdrawal of medication should not cause these symptoms.

Dosage and Administration. For most patients with illness of mild to moderate severity, a starting daily dose of 75 mg is recommended. Dosage may subsequently be increased or decreased at appropriate intervals and according to individual response. The usual optimum dose range is 75 mg/day to 150 mg/day.

In more severely ill patients higher doses may be required with subsequent gradual increase to 300 mg/day if necessary. Additional therapeutic effect is rarely to be obtained by exceeding a dose of 300 mg/day.

In patients with very mild symptomatology or emotional symptoms accompanying organic disease, lower doses may suffice. Some of these patients have been controlled on doses as low as 25-50 mg/day.

The total daily dosage of SINEQUAN may be given on a divided or once-a-day dosage schedule. If the once-a-day schedule is employed the maximum recommended dose is 150 mg/day. This dose may be given at bedtime. **The 150 mg capsule strength is intended for maintenance therapy only and is not recommended for initiation of treatment.**

Anti-anxiety effect is apparent before the antidepressant effect. Optimal antidepressant effect may not be evident for two to three weeks.

Overdosage.

A. Signs and Symptoms

1. Mild: Drowsiness, stupor, blurred vision, excessive dryness of mouth.
2. Severe: Respiratory depression, hypotension, coma, convulsions, cardiac arrhythmias and tachycardias.

Also: urinary retention (bladder atony), decreased gastrointestinal motility (paralytic ileus), hyperthermia (or hypothermia), hypertension, dilated pupils, hyperactive reflexes.

B. Management and Treatment

1. Mild: Observation and supportive therapy is all that is usually necessary.
2. Severe: Medical management of severe SINEQUAN overdose consists of aggressive supportive therapy. If the patient is conscious, gastric lavage, with appropriate precautions to prevent pulmonary aspiration, should be performed even though SINEQUAN is rapidly absorbed. The use of activated charcoal has been recommended, as has been continuous gastric lavage with saline for 24 hours or more. An adequate airway should be established in comatose patients and assisted ventilation used if necessary. EKG monitoring may be required for several days, since relapse after apparent recovery has been reported. Arrhythmias should be treated with the appropriate antiarrhythmic agent. It has been reported that many of the cardiovascular and CNS symptoms of tricyclic antidepressant poisoning in adults may be reversed by the slow intravenous administration of 1 mg to 3 mg of physostigmine salicylate. Because physostigmine is rapidly metabolized, the dosage should be repeated as required. Convulsions may respond to standard anticonvulsant therapy, however, barbiturates may potentiate any respiratory depression. Dialysis and forced diuresis generally are not of value in the management of overdose due to high tissue and protein binding of SINEQUAN.

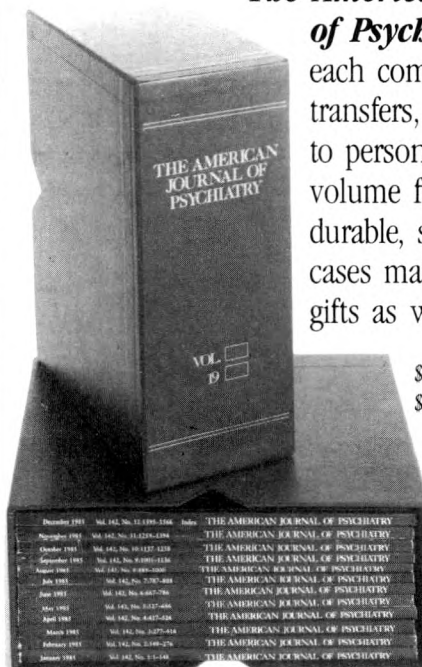
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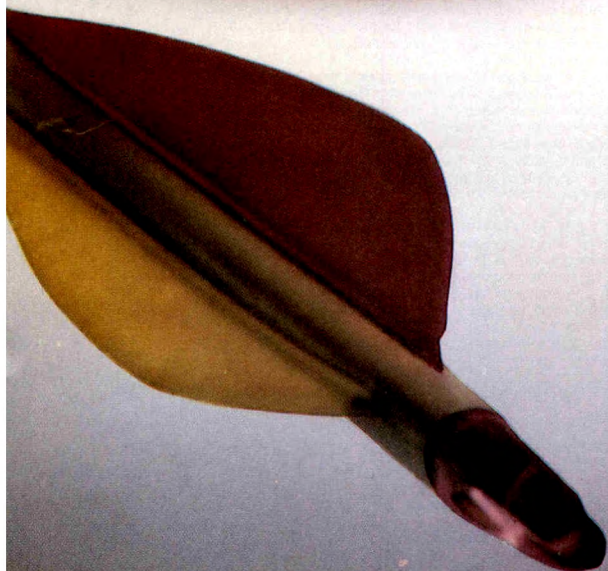
On-target control of psychosis

"The least potent antipsychotics (chlorpromazine and thioridazine) tend to be the most sedating and to have the most anticholinergic effects."¹

LOXITANE provides moderate sedation and causes fewer anticholinergic effects than lower potency neuroleptics²—less than 1% incidence of hypotension or syncope in clinical trials.³

"The relatively more potent agents, especially haloperidol and fluphenazine, cause the highest incidence of side effects in the extrapyramidal system."¹

LOXITANE causes fewer extrapyramidal effects than more potent neuroleptics.²



Aim for the Center

LOXITANE[®]

loxapine succinate/hydrochloride

Please see the next page for a brief summary of prescribing information.

LOXITANE[®]

loxapine succinate/hydrochloride



Available in three forms for easier dosing

LOXITANE IM

loxapine hydrochloride Intramuscular
50 ml base/ml—Each ml contains the equivalent
of 50 mg loxapine base as the HCl

LOXITANE C

loxapine hydrochloride Oral Concentrate
25 mg base/ml in bottles of 4 fl oz

LOXITANE loxapine succinate Capsules
5 mg, 10 mg, 25 mg, 50 mg

All dosage forms with milligram-for-milligram
equivalency

LOXITANE[®] loxapine succinate Capsules
LOXITANE[®] C loxapine hydrochloride Oral Concentrate
LOXITANE[®] IM loxapine hydrochloride

INDICATIONS: LOXITANE is indicated for the management of the manifestations of psychotic disorders. The antipsychotic efficacy of LOXITANE was established in clinical studies which enrolled newly hospitalized and chronically hospitalized acutely ill schizophrenic patients as subjects.

CONTRAINDICATIONS: Comatose or severe drug-induced depressed states (alcohol, barbiturates, narcotics, etc); hypersensitivity to the dibenzoxazepines.

WARNINGS: *Tardive Dyskinesia:* Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may develop in patients treated with neuroleptic (antipsychotic) drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of neuroleptic treatment, which patients are likely to develop the syndrome. Whether neuroleptic drug products differ in their potential to cause tardive dyskinesia is unknown.

Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dosage of neuroleptic drugs administered to the patient increases. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low dosages.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if neuroleptic treatment is withdrawn. Neuroleptic treatment itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome, and thereby may possibly mask the underlying disease process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, neuroleptics should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic neuroleptic treatment should generally be reserved for patients who suffer from a chronic illness that (1) is known to respond to neuroleptic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dosage and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on neuroleptics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome.

Mental and/or physical abilities may be impaired, especially during early therapy; warn ambulatory patients about activities requiring alertness, about concomitant use of alcohol and other CNS depressants. Not recommended for management of behavioral complications in mentally retarded patients.

PRECAUTIONS: Use with extreme caution in patients with a history of convulsive disorders; seizures have been reported in epileptic patients receiving antipsychotic dosage levels and in epileptic patients with maintenance of anticonvulsant therapy. Use with caution in patients with cardiovascular disease or in those with glaucoma or a tendency to urinary retention, particularly when on concomitant anticholinergic medication. Loxapine has an antiemetic effect in animals which might occur in man, masking signs of overdosage of toxic drugs and obscuring intestinal obstruction or brain tumor. Since possible ocular toxicity cannot be excluded, observe carefully for pigmentary retinopathy and lenticular pigmentation. Slightly higher incidence of extrapyramidal effects possible following IM administration than normally anticipated with oral formulations.

Neuroleptic drugs elevate prolactin levels; elevation persists during chronic administration. Tissue culture experiments indicate that approximately one third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of neuroleptic drugs. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time.

Safe use during pregnancy or lactation or by women of child-bearing potential has not been established; weigh potential benefits against possible risks to mother and child. No embryotoxicity or teratogenicity was observed in studies in rats, rabbits, or dogs, although, with the exception of one rabbit study, the highest dosage was only two times the maximum recommended human dosage, and in some studies it was below this dosage. Perinatal studies have shown renal papillary abnormalities in offspring of rats treated from midpregnancy with doses of 0.6 to 1.8 mg/kg doses which approximate the usual human dose but which are considerably below the maximum recommended human dose. It is known that this drug and its metabolites have been transported into the milk of lactating dogs. LOXITANE[®] loxapine administration to nursing women should be avoided, if clinically possible. Not recommended for use in children under 16.

ADVERSE REACTIONS: *CNS Effects:* Other than extrapyramidal, have been seen infrequently. Drowsiness, dizziness, faintness, staggering gait, shuffling gait, muscle twitching, weakness, insomnia, agitation, tension, seizures, akinesia, slurred speech, numbness, and confusional states have been reported. Neuroleptic malignant syndrome (NMS) has been reported. *Extrapyramidal Reactions:* Neuromuscular (extrapyramidal) frequently, often during the first few days of treatment. Reactions involved parkinsonian-like symptoms such as tremor, rigidity, excessive salivation, and masked facies. Akathisia (motor restlessness) also has been reported relatively frequently. Dystonic and dyskinetic reactions have occurred less frequently, but may be more severe. Dystonias include spasms of muscles of the neck and face, tongue protrusion, and oculogyric movement. Dyskinetic reactions have been described in the form of choreoathetoid movements. These reactions sometimes require reduction or temporary withdrawal of loxapine dosage in addition to appropriate counteractive drugs.

Persistent Tardive Dyskinesia: As with all antipsychotic agents, tardive dyskinesia may appear in some patients on long-term therapy or may appear after drug therapy has been discontinued. Risk appears to be especially greater in elderly female patients on high-dosage therapy. Symptoms are persistent and in some patients appear to be irreversible. Syndrome is characterized by rhythmic involuntary movement of the tongue, face, mouth, or jaw (eg, protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities. *Cardiovascular Effects:* Tachycardia, hypotension, hypertension, orthostatic hypotension, lightheadedness, and syncope. A few cases of ECG changes have been reported. *Hematologic:* Rarely, agranulocytosis, thrombocytopenia, leukopenia. *Skin:* Dermatitis, edema (puffiness of face), pruritus, rash, alopecia, and seborrhea. *Anticholinergic Effects:* Dry mouth, nasal congestion, constipation, blurred vision, urinary retention, and paralytic ileus. *Gastrointestinal:* Nausea, vomiting, and hepatocellular injury (ie, SGOT/SGPT elevation). Rarely, jaundice and/or hepatitis. *Other:* Weight gain, weight loss, dyspnea, ptosis, hyperpyrexia, flushed facies, headache, paresthesia, and polydipsia. Rarely, galactorrhea, amenorrhea, gynecomastia, and menstrual irregularity of uncertain etiology. **OVERDOSAGE:** Signs and symptoms are those expected from the pharmacological actions and amount ingested. Can range from mild depression of CNS and cardiovascular symptoms to profound hypotension, respiratory depression and unconsciousness. Extrapyramidal symptoms and convulsive seizures have occurred as well as renal failure. Treatment is essentially symptomatic and supportive. Early gastric lavage with dialysis might be expected to be beneficial. Avoid use of centrally acting emetics, analeptics, and epinephrine.

Rev. 1/86

References:

- Thompson TL II, Moran MG, Nies AS: Psychotropic drug use in the elderly. *New Engl J Med* 1983; 308: 194-198.
- Rhoades HM, Overall JE: Side effect potentials of different antipsychotic and antidepressant drugs. *Psychopharmacol Bull* 1984; 20:83-88.
- Data on file, Lederle Laboratories, Pearl River, N.Y.

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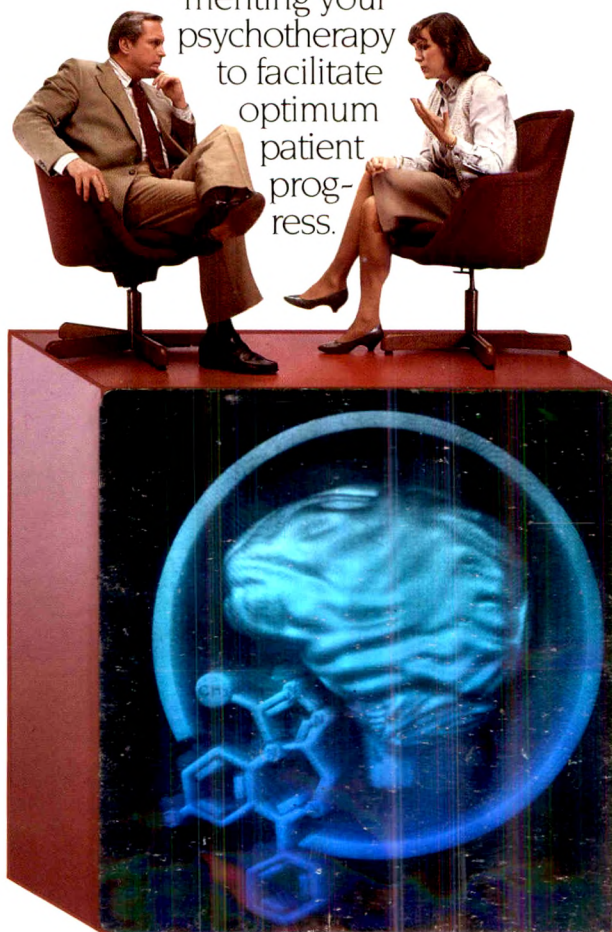
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Xanax[®] 0.5 mg
alprazolam ^{IV} Tablets

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Xanax[®] 0.5 mg
alprazolam ^{IV} Tablets

XANAX[®] Tablets (alprazolam) ^{IV}

CONTRAINDICATIONS

Patients with sensitivity to this drug or other benzodiazepines and in acute narrow angle glaucoma.

WARNINGS

Not of value in psychotic patients. Caution patients against hazardous occupations requiring complete mental alertness and about the simultaneous ingestion of alcohol and other CNS depressant drugs.

Benzodiazepines can cause fetal harm in pregnant women. Warn patients of the potential hazard to the fetus. Avoid during the first trimester.

PRECAUTIONS

General: The dosage of XANAX Tablets should be reduced or withdrawn gradually, since withdrawal seizures have been reported upon abrupt withdrawal. If XANAX is combined with other psychotropics or anticonvulsant drugs, consider drug potentiation (see Drug Interaction section). Exercise the usual precautions regarding size of the prescription for depressed or suicidal patients. In elderly and debilitated patients, use the lowest possible dosage (see Dosage and Administration). Observe the usual precautions in treating patients with impaired renal or hepatic function.

Information for Patients: Alert patients about: (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing dose of the drug due to risk of dependence, (e) not stopping the drug abruptly. **Laboratory Tests:** Not ordinarily required in otherwise healthy patients. **Drug Interactions:** Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistamines, ethanol and other CNS depressants. Pharmacokinetic interactions with ben-

zodiazepines have been reported. **Drug/Laboratory Test Interactions:** No consistent pattern for a specific drug or specific test. **Carcinogenesis, Mutagenesis, Impairment of Fertility:** No carcinogenic potential or impairment of fertility in rats. **Pregnancy:** See Warnings. **Nonteratogenic Effects:** The child born of a mother on benzodiazepines may be at some risk for withdrawal symptoms and neonatal flaccidity. **Labor and Delivery:** No established use. **Nursing Mothers:** Benzodiazepines are excreted in human milk. Women on XANAX should not nurse. **Pediatric Use:** Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS

Side effects are generally observed at the beginning of therapy and usually disappear with continued medication. In the usual patient, the most frequent side effects are likely to be an extension of the pharmacologic activity of XANAX, eg, drowsiness or lightheadedness.

Central nervous system: Drowsiness, lightheadedness, depression, headache, confusion, insomnia, nervousness, syncope, dizziness, akathisia, and tiredness/sleepiness.

Gastrointestinal: Dry mouth, constipation, diarrhea, nausea/vomiting, and increased salivation.

Cardiovascular: Tachycardia/palpitations, and hypotension.

Sensory: Blurred vision.

Musculoskeletal: Rigidity and tremor.

Cutaneous: Dermatitis/allergy.

Other side effects: Nasal congestion, weight gain, and weight loss.

In addition, the following adverse events have been reported with the use of benzodiazepines: dystonia, irritability, concentration difficulties, anorexia, transient amnesia or memory impairment, loss of coordination, fatigue, sedation, slurred speech, jaundice, musculoskeletal weakness, pruritus, diplopia,

dysarthria, changes in libido, menstrual irregularities, incontinence and urinary retention.

Paradoxical reactions such as stimulation, agitation, increased muscle spasticity, sleep disturbances, and hallucinations may occur. Should these occur, discontinue the drug.

During prolonged treatment, periodic blood counts, urinalysis, and blood chemistry analysis are advisable. Minor EEG changes of unknown significance have been observed.

DRUG ABUSE AND DEPENDENCE

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Books Received

- Anima as Fate**, by Cornelia Brunner; translated by Julius Heuscher; edited by David Scott May. Dallas, Tex., Spring Publications, 1986, 277 pp., \$16.00 (paper).
- Postnatal Depression: A Guide for Health Professionals**, by John L. Cox, M.A., D.M., F.R.C.P. (Ed.), D.P.M., M.R.C.Psych. New York, Churchill Livingstone (White Plains, N.Y., Longman, distributor), 1986, 93 pp., \$10.00 (paper).
- Listen to Your Child: A Parent's Guide to Children's Language**, by David Crystal. New York, Penguin Books, 1986, 240 pp., \$5.95 (paper).
- Contemporary Marriage: Comparative Perspectives on a Changing Institution**, edited by Kingsley Davis in association with Amyra Grossbard-Shechtman. New York, Russell Sage Foundation (Basic Books, distributor), 1985, 414 pp., \$29.95.
- Health Planning and Social Change**, by Leonard J. Duhl; edited by Joanna Tamer. New York, Human Sciences Press, 1986, 313 pp., no price listed.
- Oral Sadism and the Vegetarian Personality: Readings From the Journal of Polymorphous Perversity**, edited by Glenn C. Ellenbogen, Ph.D. New York, Brunner/Mazel, 1986, 217 pp., \$20.00.
- Oldtimers and Alzheimer's: The Descriptive Organization of Senility**, by Jaber F. Gubrium. Greenwich, Conn., JAI Press, 1986, 219 pp., \$24.75.
- The Power Tactics of Jesus Christ and Other Essays**, 2nd ed., by Jay Haley. Rockville, Md., Triangle Press (New York, W.W. Norton & Co., distributor), 1986, 160 pp., \$14.95.
- Psychotherapy Through Clinical Role Playing**, by David A. Kipper. New York, Brunner/Mazel, 1986, 377 pp., \$40.00.
- Japanese Culture and Behavior: Selected Readings**, revised ed., edited by Takie Sugiyama Lebra and William P. Lebra. Honolulu, University of Hawaii Press, 1986, 420 pp., no price listed (paper).
- Handbook of Cognitive Therapy Techniques**, by Rian E. McMullin, Ph.D. New York, W.W. Norton & Co., 1986, 342 pp., \$34.95.
- The Matrix of the Mind: Object Relations and the Psychoanalytic Dialogue**, by Thomas H. Ogden, M.D. Northvale, N.J., Jason Aronson, 1986, 260 pp., \$25.00.
- Systems Psychology in the Schools**, by Jeanne M. Plas. New York, Pergamon Press, 1986, 156 pp., \$24.50; 12.95 (paper).
- Sexual Intimacy Between Therapists and Patients**, by Kenneth S. Pope and Jacqueline C. Bouhoutsos. New York, Praeger, 1986, 182 pp., \$29.95.
- The Infant Mind**, by Richard M. Restak, M.D. Garden City, N.Y., Doubleday & Co., 1986, 264 pp., \$18.95.
- Pediatric Psychology: Psychological Interventions and Strategies for Pediatric Problems**, by Michael C. Roberts. New York, Pergamon Press, 1986, 110 pp., \$19.50; \$10.95 (paper).
- Conducting Insanity Evaluations**, by Richard Rogers, Ph.D. New York, Van Nostrand Reinhold, 1986, 255 pp., \$34.50.
- The Language of Psychosis**, by Bent Rosenbaum and Harly Sonne. New York, New York University Press (Columbia University Press, distributor), 1986, 137 pp., \$32.00.
- The Psychobiology of Mind-Body Healing: New Concepts of Therapeutic Hypnosis**, by Ernest Lawrence Rossi. New York, W.W. Norton & Co., 1986, 220 pp., \$25.95.
- Famous and Very Important Persons: Medical Psychological Psychiatric Bibliography 1960-1984**, by Johan Schioldann-Nielsen, M.D., Dr.Med., M.R.A.N.Z.C.P. Odense, Denmark, Odense University Press, 1986, 186 pp., 200 Danish kroner (paper).
- Psychiatric Case Registers in Public Health: A Worldwide Inventory 1960-1985**, edited by G.H.M.M. ten Horn, R. Giel, W.H. Gulbinat, and J.H. Henderson. New York, Elsevier, 1986, 443 pp., \$66.75.
- Conquering Senility**, by Arthur C. Walsh, M.D. Coraopolis, Pa., J. Pohl Associates, 1985, 87 pp., \$5.95 (paper).
- Behavior Management in the Schools: Principles and Procedures**, by Richard M. Wielkiewicz. New York, Pergamon Press, 1986, 258 pp., \$38.50; \$14.95 (paper).
- Transformations of Consciousness: Conventional and Contemplative Perspectives on Development**, by Ken Wilber, Jack Engler, Daniel P. Brown, et al. Boston, New Science Library, Shambhala (New York, Random House, distributor), 1986, 343 pp., \$14.95 (paper).
- The Therapist's Thesaurus: A Cartoon Guide**, by Robert Wilkins and Penny Loudon. London, Croom Helm, and Philadelphia, Charles Press, 1987, 88 pp., \$6.95 (paper).
- The Medical Basis of Psychiatry**, edited by George Winokur, M.D., and Paula Clayton, M.D. Philadelphia, W.B. Saunders Co., 1986, 579 pp., \$60.00.
- In Support of Families**, edited by Michael W. Yogman and T. Berry Brazelton. Cambridge, Harvard University Press, 1986, 283 pp., \$25.00.

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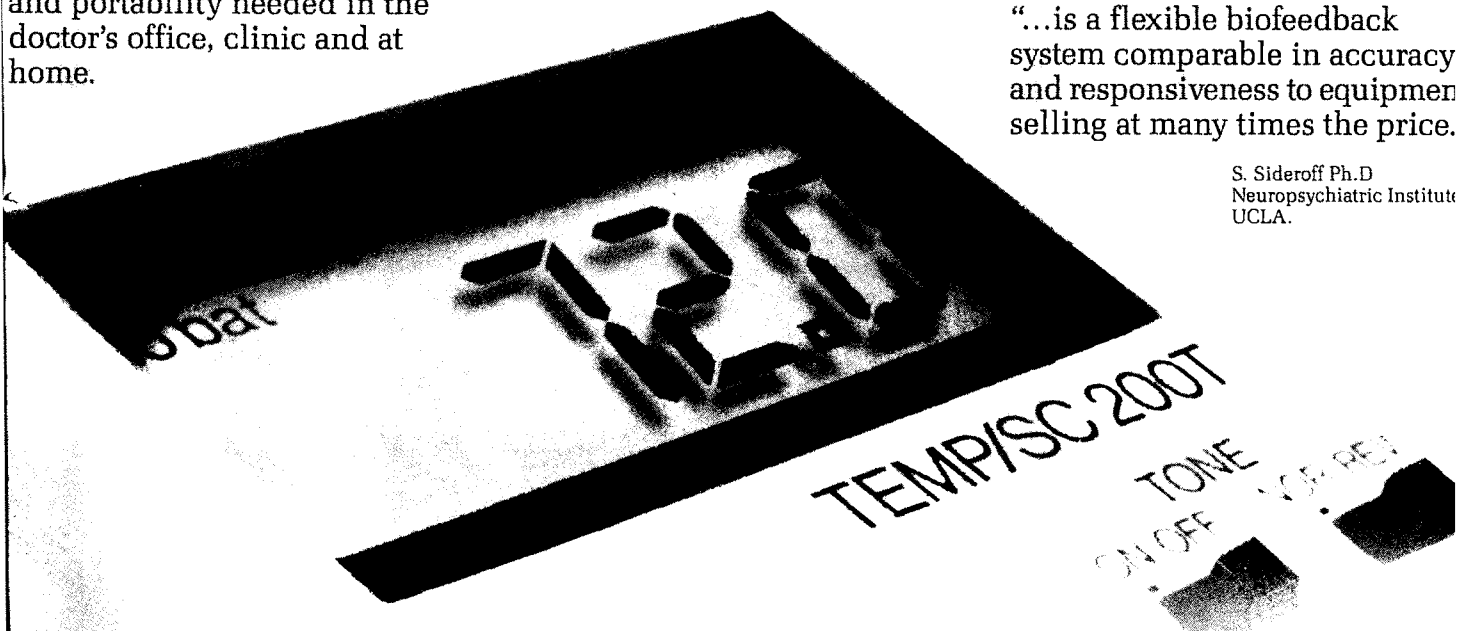
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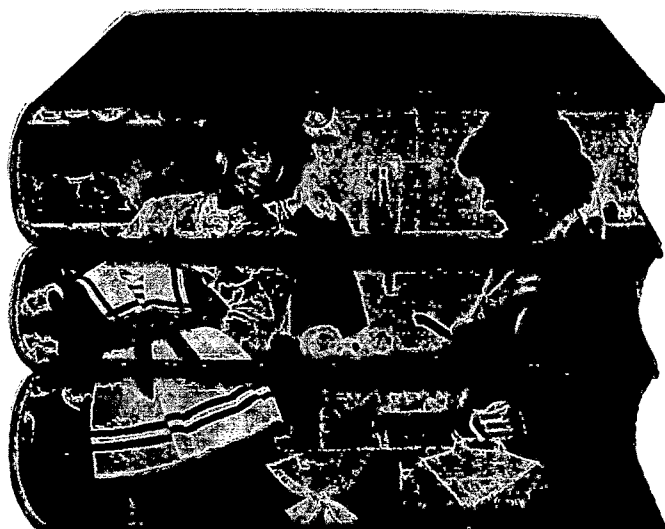
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Warnings: The risk of developing potentially irreversible *tardive dyskinesia* is believed to increase as duration of treatment and total cumulative dose increase, although it is impossible to predict who will develop the syndrome. It can also develop, although much less commonly, after brief treatment with low doses. Incidence appears to be highest among the elderly, especially elderly women. Generally chronic treatment should be reserved for chronically ill patients whose disease is most likely to respond to neuroleptic drugs and for whom other effective, less harmful treatment is not available or appropriate. There is no known treatment for *tardive dyskinesia* although the syndrome may partially or completely remit upon withdrawal of neuroleptic treatment. If signs and symptoms of *tardive dyskinesia* appear, drug discontinuation should be considered. Administer cautiously to patients who have previously exhibited a hypersensitivity reaction (e.g., blood dyscrasias, jaundice) to phenothiazines. Phenothiazines are capable of potentiating central nervous system depressants (e.g., anesthetics, opiates, alcohol, etc.) as well as atropine and phosphorus insecticides; carefully consider benefit versus risk in less severe disorders. During pregnancy, administer only when the potential benefits exceed the possible risks to mother and fetus.

Precautions: There have been infrequent reports of leukopenia and/or agranulocytosis and convulsive seizures. In epileptic patients, anticonvulsant medication should also be maintained. Pigmentary retinopathy, observed primarily in patients receiving larger than recommended doses, is characterized by diminution of visual acuity, brownish coloring of vision, and impairment of night vision; the possibility of its occurrence may be reduced by remaining within recommended dosage limits. Administer cautiously to patients participating in activities requiring complete mental alertness (e.g., driving), and increase dosage gradually. Orthostatic hypotension is more common in females than in males. Do not use epinephrine in treating drug-induced hypotension since phenothiazines may induce a reversed epinephrine effect on occasion.

Neuroleptic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent in vitro, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomasia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. Daily doses in excess of 300 mg should be used only in severe neuropsychiatric conditions.

Information for Patients: It is suggested that all patients who are candidates for chronic treatment be advised of the risk of *tardive dyskinesia*.

Adverse Reactions: *Central Nervous System*—Drowsiness, especially with large doses, early in treatment; infrequently, pseudoparkinsonism and other extrapyramidal symptoms; rarely, nocturnal confusion, hyperactivity, lethargy, psychotic reactions, restlessness, and headache. *Autonomic Nervous System*—Dryness of mouth, blurred vision, constipation, nausea, vomiting, diarrhea, nasal stuffiness,

and pallor. *Endocrine System*—Galactorrhea, breast engorgement, amenorrhea, inhibition of ejaculation, and peripheral edema. *Skin*—Dermatitis and skin eruptions of the urticarial type, photosensitivity. *Cardiovascular System*—ECG changes (see *Cardiovascular Effects* below). *Other*—Rare cases described as parotid swelling.

It should be noted that efficacy, indications and untoward effects have varied with the different phenothiazines. It has been reported that old age lowers the tolerance for phenothiazines; the most common neurological side effects are parkinsonism and akathisia, and the risk of agranulocytosis and leukopenia increases. The following reactions have occurred with phenothiazines and should be considered whenever one of these drugs is used:

Autonomic Reactions—Miosis, obstipation, anorexia, paralytic ileus. **Cutaneous Reactions**—Erythema, exfoliative dermatitis, contact dermatitis. **Blood Dyscrasias**—Agranulocytosis, leukopenia, eosinophilia, thrombocytopenia, anemia, aplastic anemia, pancytopenia. **Allergic Reactions**—Fever, laryngeal edema, angioneurotic edema, asthma. **Hepatotoxicity**—Jaundice, biliary stasis. **Cardiovascular Effects**—Changes in the terminal portion of electrocardiogram including prolongation of Q-T interval, lowering and inversion of T-wave, and appearance of a wave tentatively identified as a bifid T or a U wave have been observed with phenothiazines, including Mellaril (thioridazine); these appear to be reversible and due to altered repolarization, not myocardial damage. While there is no evidence of a causal relationship between these changes and significant disturbance of cardiac rhythm, several sudden and unexpected deaths apparently due to cardiac arrest have occurred in patients showing characteristic electrocardiographic changes while taking the drug. While proposed, periodic electrocardiograms are not regarded as predictive. Hypotension, rarely resulting in cardiac arrest. **Extrapyramidal Symptoms**—Akathisia, agitation, motor restlessness, dystonic reactions, trismus, torticollis, opisthotonus, oculogyric crises, tremor, muscular rigidity, and akinesia. **Tardive Dyskinesia**—Characterized by involuntary choreoathetoid movements variously involving the tongue, face, mouth, lips or jaw (e.g., protrusion of the tongue, puffing of the cheeks, puckering of the mouth, chewing movements), trunk and extremities—may be recognized during treatment upon dosage reduction or withdrawal of treatment. Movements may decrease or disappear if further treatment is withheld, although this reversibility is more likely after short-term rather than long-term treatment. Since neuroleptics may mask the signs of *tardive dyskinesia*, reducing dosage periodically increases the likelihood of detecting the syndrome at the earliest possible time. **Endocrine Disturbances**—Menstrual irregularities, altered libido, gynecomasia, lactation, weight gain, edema, false positive pregnancy tests. **Urinary Disturbances**—Retention, incontinence. **Others**—Hyperpyrexia; behavioral effects suggestive of a paradoxical reaction, including excitement, bizarre dreams, aggravation of psychoses, and toxic confusional states; following long-term treatment, a peculiar skin-eye syndrome marked by progressive pigmentation of skin or conjunctiva and/or accompanied by discoloration of exposed sclera and cornea; stellate or irregular opacities of anterior lens and cornea; systemic lupus erythematosus-like syndrome.

Dosage: Dosage must be individualized according to the degree of mental and emotional disturbance, and the smallest effective dosage should be determined for each patient.

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Heinz Kohut's Self Psychology: An Overview

Howard S. Baker, M.D., and Margaret N. Baker, Ph.D.

In the 16 years since its inception, self psychology has provided a comprehensive theory of psychopathology and treatment. It has articulated a new group of developmental needs and transferences: mirroring, idealizing, and alter ego. The failure of parental empathy to meet those needs during childhood results in the inability to develop intrapsychic structures that can reliably regulate self-esteem and calm the self, leaving the person overly dependent on those in the surround to provide those functions. Treatment requires careful understanding of the early failures and provides an environment in which the intrapsychic structures may belatedly and effectively develop.

(Am J Psychiatry 1987; 144:1-9)

In their recent review, "The Cutting Edge in Psychiatry," Strauss et. al. (1) surveyed leading American psychiatrists for their views on the most important developments in their field in the last decade. Only 13 books and one journal article were listed by the respondents often enough to be considered the most important publications, and only one author was mentioned twice: Heinz Kohut, for *The Analysis of the Self* (2) and *The Restoration of the Self* (3).

These and other works by Kohut and his colleagues have formed the basis of self psychology. This substantive departure from traditional, psychoanalytically based thinking has precipitated a firestorm of controversy, challenging fundamental precepts about both the etiology and the treatment of psychopathology.

Central to traditional analytic thinking is Freud's

abandonment of the seduction theory, which he replaced with the conflicted and conflicting drives of the Oedipus complex. He came to believe that the parents of most patients do not actually abuse their children to fulfill their own needs. Rather, faulty resolution of the oedipal conflict results in the child's projecting unwanted, repressed feelings onto the parents. The crucial issue in the pathogenesis of neurosis is the unsatisfactory resolution of the child's conflicted drives, not the parents' failure to properly respond to the child.

While Kohut has no doubt that conflicts, particularly oedipal conflicts, exist, he holds that they would be resolved without neurotic defenses were it not for the failure of parents to meet certain essential needs of the child. Kohut has gone so far as to state: "We could say that after an eighty-year-long detour, we are returning to Freud's original seduction theory—though not in the form in which Freud had entertained it. The seduction that we have in mind related not to overt sexual activities of the adult . . . but to the fact that the [parents' empathic responsiveness to their children] is distorted in a specific way" (4, p. 11). These actual failures are unintended and beyond the parents' control, having as their root cause the psychological limitations of the parents themselves.

Kohut has also challenged a fundamental assumption about what produces therapeutic change. He concluded that insight, while important, is not the crucial element. "Whereas traditional analysis has advanced interpretation as the psychoanalyst's basic therapeutic action, Kohut emphasizes the analyst's creation of a new kind of experience for the patient within the transference relationship, of which interpretation is only a facet" (5).

While these and other positions have seemed so controversial to many analysts, Palaci (6), Basch (7), and others consider that these changes merely reflect the way that many good psychotherapists who have never read the self psychology literature have come to practice. It has repeatedly come to our attention that many of these clinicians would like to be better in-

Received July 15, 1985; revised Dec. 20, 1985; accepted Feb. 13, 1986. From the Department of Psychiatry, University of Pennsylvania; Drexel University; and the Department of Psychology, Hahnemann University, Philadelphia, Pa. Address reprint requests to Dr. Howard Baker, 1103 Spruce St., Philadelphia, PA 19107.

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formed but have found the self psychology literature contradictory, even impenetrable.

Much of this confusion is a consequence of the evolution of thinking about psychopathology over the 16 years since the publication of Kohut's first book. Initially, he was concerned primarily with the narcissistic problems of patients with behavior and character disorders. More experience led him and his colleagues to realize that essential elements of self psychology were applicable to psychoses, borderline states, and the neuroses. While he did not adequately address the issues of biological predisposition, Kohut concluded that it was the earliness and extensiveness of the empathic failures of the parents and parental substitutes which differentiated patients in the diagnostic categories cited earlier. He thought that developmental arrests which inevitably resulted from parental shortcomings most comprehensively and helpfully explained psychopathology. This stands in opposition to the concept that psychopathology reflects inadequately resolved conflict (producing symptoms which are disguised attempts at gratification of drives) or developmental regressions to points where the conflicts could be more successfully resolved.

While self psychology has never denied the existence of the drives or of conflict, it has now placed them in an entirely different context. It proposes such a substantially different view of these issues that it offers a virtually new, comprehensive view of psychological life—one that its practitioners obviously consider offers important therapeutic advantages.

EMPATHY

Self psychology holds that parents' inability to appropriately empathize with their children causes the parenting failures noted earlier. Although parents are usually not purposely unresponsive, children must adapt—or maladapt—to parental treatment. Repeated empathic failures by the parents, and the child's responses to them, are at the root of almost all psychopathology.

Kohut and other psychoanalysts have long emphasized the importance of empathy, but it was in the case of Miss F. (2) that Kohut initially emphasized the crucial role of empathy in healthy and pathologic development as well as in the facilitation of psychotherapeutic cure. Miss F. greeted Kohut's carefully thought-out traditional interpretations with fury and the repeated comment, "You are ruining my analysis with these interpretations." For a considerable time he understood her protestations as resistance and was confident about the accuracy of his understanding. Eventually he realized that he had failed to put himself empathically in her position—imposing *his* theory on *her* situation.

The *American Heritage Dictionary* defines empathy as "understanding so intimate that the feelings, thoughts and motives of one are readily comprehended

by another." It is not to be confused with being nice to someone. Empathy is to intrinsically comprehend the experience of others from their own unique perspective, which is often very different from "what I would feel if I were actually in their place." Empathy has the potential to enable someone to respond in a helpful, responsible way or in a destructive way. It has both affective and cognitive elements—one feels what the other feels and then, through a complex, not necessarily conscious process, becomes aware what the other is feeling.

SELF-OBJECTS AND SELF-OBJECT RELATIONSHIPS

These crucial empathic failures occur as a normal aspect of human interaction that Kohut called self-object relationships. He realized that Miss F. did not experience him as a separate person. Rather, she seemed to need him to be an extension of herself, someone over whom she had a degree of control normally reserved for a part of one's body like one's hand. She demanded that his responses instantly and totally fulfill certain needs (see following discussion) which she genuinely could not meet herself. Kohut labeled these internal needs, which must be at least partially met by another person, *self-object* needs.

Kohut tried to distinguish self-object needs from object needs. In the latter, the other person functions as an autonomous object, an independent center of initiative. Objects are valued for who they are. Self-objects are valued for the internal functions and the emotional stability they provide. The self-object need's being met is more important than who meets it.

The essential element of Miss F.'s psychopathology was her absolute reliance on the responses of others (both the analyst and the people in her surround) to maintain her self-esteem. That is, for her, people primarily had to function not as objects but as self-objects. She needed others to reassure her or she would experience catastrophic loss of self-esteem.

An old slogan of the American Dairy Association proclaims: "You never outgrow your need for milk." The same is true of empathically accurate self-objects. We always need them, although they undergo developmental maturing. Kohut strongly held that, in addition to the generally accepted line of object development, there is a parallel line of self-object development. In infancy, self-object needs are absolute and intense and must be externally met, primarily by the mother. Throughout childhood, increasing distance from the mother is tolerated. The father's role becomes more important, and parental substitutes (like grandparents, teachers, friends, and neighbors) are willingly accepted. During adolescence, the peer group is a crucial self-object. In adulthood, the spouse, friends, and careers may be self-objects. In addition to broadening who or what may serve as self-objects, the healthy individual develops reliable, consistent, and endopsychic structures which assume many of the functions

that were previously required of external self-objects. The person becomes more internally competent, less externally needy, and more flexible in meeting the remaining self-object needs.

SELF-OBJECT TRANSFERENCES AND NEEDS: MIRRORING

Miss F. and other patients led Kohut to formulate a new group of transferences that reflect unmet self-object needs. Initially, he formulated two major types of self-object transferences, mirroring and idealizing. Eventually he added a third, the alter ego, or twinship, transference.

Miss F. primarily demonstrated the mirroring transference. Just as she looked into the mirror to see how she appeared as she combed her hair, she constantly and intensely turned to Kohut's responses to determine how valuable, good, and worthy she was. Any response that did not seem totally approving was intolerable and shattered her self-esteem.

Miss F. and other people with problems in this area have experienced repeated and significant mirroring failures from their parents or parental substitutes. While these failures often continue into the present, the crucial ones occurred during childhood. Early, pervasive self-object failures produce the most severe developmental arrests, greater reliance on archaic self-object relationships, and a predisposition to more severe psychopathology.

The delighted response of the parents to the child—the gleam in the mother's eye—is essential to the child's development. This response mirrors back to the child a sense of self-worth and value, creating internal self-respect. Parental responses of indifference, hostility, or excessive criticism reflect back low worth and consequently inhibit the child's assertiveness. The mirroring responses of the parent are concerned with the maintenance and development of self-esteem and self-assertive ambitions.

Any parent knows that all of the child's needs cannot be met and that all of the child's wishes should not be met. It is an accomplishment for a 2-year-old to throw a ball regardless of where it lands. An admiring response for the same feat accomplished by an 8-year-old is inaccurate and therefore destructive. To be fully empathic, the mirroring response must be developmentally appropriate and genuine.

Children may seek interaction with an exhausted parent who is simply too tired to respond. They will sometimes be rebuffed by the reality of the parent's fatigue. Should these inevitable "failures" in parental self-object responses become overwhelming, the child may try to compensate for a lack by trying to be perfect, cute, bright, or wonderful. This attempt to "fix" the insult reflects the child's perception that something is wrong with him or her; the child believes that the lack of mirroring responses, which would have affirmed the child's sense of self, is caused by his or her

inadequacy. Self psychology refers to the effort to be perfect as the "grandiose, exhibitionistic self." In the context of a generally responsive environment (the "good enough" parents), the intensity of the grandiose self is diminished but not destroyed. "In other words, given reasonable care, humans are so constituted that they preserve a 'piece of the old grandiose delusion' . . . , in spite of the fact, and even because of the fact, that from the beginning of life a countless number of inevitable in phase ('optimal') frustrations and injuries begin to modulate and transform these delusions by teaching us the limits of our own and other's power" (8). It is these optimal failures which require the child to develop or invent internal means to maintain self-esteem, tolerate unavoidable failure, and pursue appropriate ambitions with vigor. The developing child's self-object needs can then mature from archaic demands for perfection and constant attention to self-confidence and the healthy self-object need for occasional, thoughtful appreciation and praise.

Clinically, we do not see the results of the "failures" of good enough parents. Instead, we see people for whom the parent-child interaction seriously failed to meet the child's self-object needs. This occurs for some combination of these three reasons: 1) the child has exquisite needs due to such factors as genetic predispositions, physical handicaps, or learning disabilities; 2) there is an unfortunate mismatch between the temperaments of the parent and the child (9); and 3) the parent has serious limitations in his or her ability to respond adequately for various reasons, including the parent's own psychopathology and externally imposed circumstances (e.g., death of another child, job loss, illness). There is a complex interaction, a feedback process between parent and child that results in a "continuous modification of both. The relationship, therefore, is gradually changed over time" (10). A deteriorating process may ensue, and whatever the reason, there may be repeated, actual failure in meeting the child's legitimate self-object needs. Consequently, the child is impeded in developing internal structures to regulate self-esteem.

Several examples will clarify the concepts of good enough and pathogenic mirroring. Marion Tolpin (11) has described an incident with a friend's 5-year-old child: he was learning to skate with his parents' help and delighted encouragement. On a school outing, he tried to skate when his parents were not present and failed miserably. His parents' approving presence was necessary for him to be able to function adequately—they almost literally firmed up his ankles. When an expectable, unavoidable disruption in the needed self-object relationship occurred in the context of this reasonably empathically responsive family, this minor failure to meet the child's needs probably resulted in a small bit of growth. The child's grandiosity was both preserved and tempered.

This contrasts with the case of a young man who was flunking out of college. His father was not pleased about his son's getting into a prestigious school, and

his final words to him, as he left home for the first time, were: "Just don't come around here acting fancy and driving some big car" (12). That comment is an obvious example of a continuous and destructive mirroring pattern: the father's own narcissistic vulnerability and competitiveness prevented him from enjoying and encouraging his son's success. The distortions in the father's personality made him like a fun-house mirror. Whatever the son did, the reflection was negative. As a result, the son had serious problems maintaining self-esteem and acting assertively.

While the preceding is a blatant example, destructive interchanges more frequently occur in subtle ways. A female patient remembers that her mother was delighted at what a "good child" she was. She never made any demands on her mother, who used to let her spend hours every day playing alone in the fenced-in yard while she herself pursued her personal interests. This benign neglect provided a mirror that said, "You are not a source of joy and pleasure." In adulthood, it was not natural for this patient to value or enjoy her many substantial accomplishments, nor could she accept real affection as genuine.

There are three basic personality types that result from consistent shortcomings in mirroring self-object relationships. Individuals with merger-hungry personalities must continuously attach themselves to self-objects in such an entangled way that they are often unable to "discriminate their own thoughts, wishes and intentions from those of the selfobjects" (13). Those with contact-shunning personalities avoid social interaction and become isolated because they fear that they will be swallowed up or that further nonempathic mirroring will destroy the remnants of their already vulnerable nuclear self. Finally, and generally suffering from less profound self pathology, are individuals with mirror-hungry personalities. They are compelled to insistently display themselves in such a way as to obtain continuous confirming and admiring responses, without which they feel worthless. Because of the intensity of their needs, their conviction that the needs will not be met, and the shame they feel, all of these people often alternate between depressed, hopeless withdrawal and outbursts of enraged acting out.

IDEALIZING NEEDS AND TRANSFERENCES

In addition to mirroring needs and transferences, people have what Kohut called "idealizing" requirements. These deal with our need to merge with, or be close to, someone who we believe will make us safe, comfortable, and calm. The child who falls and bumps a knee runs to a parent for a kiss, which, through no known medical process, has profound healing powers—the pain disappears! Again, an external object serves as internal function—calming and comforting—and so functions as a self-object for the child. Basch (14) has likened this to the genie in Aladdin's lamp, who could always be counted on to provide help,

protection, and comfort. Kohut referred to this all powerful self-object as the "idealized parental imago."

As with other self-object needs, there is a developmental process of maturation of the idealizing needs. Initially there is a wish to merge with the idealized parental imago; then there is a wish to be very near a source of such power; eventually the mature person is satisfied knowing that friends and family are available in times of stress. The intensity of the self-object needs decreases as the internal capacities increase—as the child creates ways first to calm the self when upset or overstimulated. Later the idealized self-objects facilitate the endopsychic abilities to control and channel libidinal and aggressive drives, and during the oedipal period contacts with the parents help the child set the beginnings of meaningful goals for life (10).

As with mirroring, a good enough parental environment is necessary for the idealizing developmental line to mature successfully. Minor failures create the need for internal structures, while basic success creates a secure enough environment to permit growth. Internal structures develop like muscles—some resistance adds power and bulk. No challenge yields atrophy, and excess exhausts, or can even tear, the muscle.

Willie Loman in Arthur Miller's *Death of a Salesman* seems to the younger son Biff to be the perfect hero. But when Biff suddenly and dramatically discovers his father's weakness and infidelity, he collapses and loses all sense of direction. There have always been problems between Biff and Willie: with machine-gun-like insistence, Willie demands that Biff do things his way; Willie does not encourage gradual, increasing independence; finally, and most dramatically, Willie's failures emerge in a traumatic way, rather than in a phase-appropriate, nontraumatic fashion. It is not lack of love but the personal limitations of the parents that caused the symptomatic son.

TWINSHIP/ALTER EGO NEEDS AND TRANSFERENCES

In his last book, Kohut thought it useful to consider a third area of self-object needs, twinship or alter ego. Here he was concerned with the need to feel a degree of likeness with other people. The small boy may stand by his father when he shaves. The son also "shaves," using a bladeless razor. These sorts of experiences lead to a feeling of being like others, of being a part of and connected to the human community.

Initially, the closeness sought may have a merged quality, but with development, greater toleration for being different is accepted. In the adolescent peer group, with its often strict dress codes, the T-shirts with the names of rock groups, and so forth, difference is often threatening. In mature adulthood, we enjoy a feeling of collegial closeness with professional organizations, take pride in a winning sports team, and so forth, but at the same time we respect and can be respected for having differences.

As with mirroring and idealizing needs, trust and closeness to the parents are essential, as is gradually increasing autonomy. If parents cannot provide activities to participate in with their children, the result is often that the child reacts defensively by being aloof and rejecting or by becoming an insistent clone.

A female patient was struggling with her relationships with other women. She could not understand why she permitted sexual contact with a particular friend and stated, "What I really want is just a sister." It emerged that she actually longed for a clone-like sense of twinship with this woman. Throughout her childhood she felt isolated and different. She was a tomboy, enjoyed playing with boys, and hated to play girls' games. Her father was cold and distant, and her more available mother was obsessed with trying to get her to behave like a girl. Being a girl meant wearing pretty dresses and not playing baseball. The absence of satisfactory twinship self-objects in childhood produced a distorted and intensified need for a twin in adulthood, and (as is often the case with these and other unmet self-object needs) the longing became sexualized.

NATURE AND DEFINITION OF THE SELF

"The concept of the self was derived from empirical data as a clinical matter of necessity; it was not invoked as an abstract scientific concept" (6, p. 323). Therefore, we must come to some useful understanding of "self" as it is used in self psychology.

The self in the broad sense of the term is "the center of the individual's psychological universe" (3, p. 311). It is what "I" refers to when we say, "I feel such and such, and I do so and so." We may describe the nature of what the self experiences and the actions that the self undertakes as a consequence of those experiences. Kohut did not believe it was possible (or necessary) to go further in defining the essence of the self (3).

Stolorow (15) has underscored the dual nature of the self: 1) a psychological structure which organizes the way we experience ourselves and 2) an existential entity which initiates and undertakes actions based on how we are experiencing ourselves—the "I" that experiences itself and the "I" that takes action. Not separating them can confuse an already complicated concept.

If the self is healthy, if during the course of the child's development there was a sufficient self-object environment, internal structures develop and there is consistency and clarity of patterns of experience and behavior even in the face of considerable stress. The healthy self can internally regulate self-esteem, calm and sooth the self, and so forth. As a consequence of these effective internal structures, others may serve as self-objects in a mature, limited way. The unhealthy self is to varying degrees dependent on self-objects to do what those underdeveloped intrapsychic structures cannot do. The self-object relationships remain archaic

and generally interfere with interpersonal functioning: e.g., a husband's archaic demands on his wife for continuous, selfless attention often will disrupt the relationship, preventing or interfering with both object love and the development of mature self-object relations (normal support).

When the unhealthy self experiences a disruption of a self-object relationship or a narcissistic insult, even though it may seem very minor to the outside observer, the self may experience depleted depression or disintegration anxiety. Kohut was unambiguous in his assertion that disintegration anxiety "is the deepest anxiety man can experience" (4, p. 16). It is similar to the fear of death, except that what is feared is not physical annihilation but loss of humanness: psychological death. Patients describe this in a variety of ways. Some feel they are falling apart, some that they are lost in space without any supply of oxygen, others that they are treading water in the middle of the ocean with nothing solid to touch, no one nearby, and the ever-present danger of sharks; still others feel dead. In its more minor forms or when the anxiety is well defended, the experience may be just one of boredom or sleepiness.

The self-experience of fragmentation or enfeebled depression causes the self-as-initiator-of-action to do something to end (or to develop some defense mechanism against) those intolerable states: to restore to the self-experience a sense of coherence, wholeness, or vigor. Even if the behavior employed to ward off disintegration anxiety is self-defeating or self-destructive, it is experienced by the individual as preferable to disintegration anxiety or depleted depression. From a self psychological point of view, then, most symptomatic behavior is viewed as an emergency attempt to maintain and/or restore internal cohesion and harmony to a vulnerable, unhealthy self.

THE TRIPOLAR SELF AND ITS DEVELOPMENT

Self psychology holds that as a result of accurate mirroring, a child develops a sense of ambition and enthusiasm for life. As a result of being able to idealize parents and draw strength and comfort from that idealization, a child develops self-direction and an ability to set challenging but realistic goals. The ambitions and goals represent the two poles of what Kohut called the "bipolar self" (3). Connecting these poles is the particular pattern of talents and skills that to a greater or lesser extent enable the ambitions to turn into achieved goals. More recently, Kohut (4) considered that the pattern of talents and skills should be considered a pole more or less equal with the ambitions and goals. It is thus more reasonable to think of a "tripolar self." This third pole develops from the twinship or alter ego self-object relationships described earlier.

For psychopathology to develop, the child must experience a fairly repeated pattern of difficulty in at

least two of the three poles of the self—mirroring, idealizing, and alter ego (4). If, for example, the parenting environment is extremely defective in providing satisfactory mirroring, the child may turn to satisfactorily available sources of idealizing and alter ego supplies. In such a case, while development might not be entirely normal statistically, the person may be able to lead a symptom-free, happy, and effective life.

The intrapsychic structures that maintain self-esteem, calm the self, and so forth are developed through a process which Kohut called “transmuting internalization.” He coined this term to differentiate it from identification, which often refers to a wholesale, or total, internalization of another person (16). In transmuting internalization, bits and pieces of the important self-object are internalized. They may be altered by the child’s inventions and are then reassembled in a unique way by the child to meet his or her psychological needs. Kohut compared the process to the body’s digestion of proteins: proteins, after ingestion, are broken down into amino acids, then absorbed and reintegrated into new or similar proteins.

DRIVES, CONFLICTS, AND THE OEDIPUS COMPLEX

It is obvious to most observers of human nature that people have what are called sexual and aggressive drives and that these drives are often both in conflict and unconscious. Self psychology has no disagreement with this. However, conflict that results in psychopathology is different from the inevitable stuff of life. The problematic drives, fears, and conflicts that our patients experience have been intensified and distorted in their childhood as a consequence of parental and environmental self-object failure (17). Kohut considered such intensified drives and conflicts to be breakdown products of self-object failure (3, 4).

There is, for example, a difference between anger or aggression and rage. Whereas aggression and anger are considered normal, healthy aspects of life, rage is a breakdown product of self-object failure (4, 18). Aggression is directed against objects, not self-objects, that is, against people or things which are experienced as autonomous centers of initiative, not against people or things serving internal self-object functions. Aggression seeks to remove whatever obstruction may exist to meeting and/or gratifying object-related drives. It subsides when the need is met, when the goal is achieved. We may get angry at a recalcitrant nail that will not go into a wall when we try to hang a picture. However, when the nail finally yields and the picture is hung, the anger subsides.

On the other hand, if the nail provokes what is experienced as narcissistic injury, if it makes us feel incompetent, we might slam the nail, damage the wall with the hammer, and feel terrible for hours. Narcissistic rage seeks revenge for the disruption of a vital self-object tie or redress against a narcissistic insult even though the outside observer, or the person him-

self, may consider the insult trivial. Rage is not satisfied with reestablishing the self-object tie or ending the insult. It pushes us to get even, to destroy the source of frustration, often without caring about the damage that may result to the self or others. In literature, Captain Ahab’s uncontrollable urge to destroy Moby Dick provides a clear example of the lengths to which a person driven by narcissistic rage may go. Ahab lost his life and the lives of most of his crew and destroyed his vessel as well!

Kohut also reformulated the nature of the oedipal phase. In the traditional view, the central issue is the appearance of phase-specific, unconscious fantasies that are related to the maturation of the sexual and aggressive drives. “As was true with regard to earlier phases of development, [what happens to these drives becomes] understandable only when they are considered within the matrix of the empathic, partially empathic, or unempathic responses from the side of the self-object aspects of [the] environment [during the oedipal period]” (3, p. 230). Kohut considered the oedipal *phase*, marked by the normal, not necessarily problematic, sexual attachment to the heterogenital parent and aggressive and competitive feelings toward the homogenital parent, to be inevitable during the oedipal *period*. However, for an oedipal *complex* to develop, for those drives to produce substantially unresolved conflict, parents must fail, in a significant manner, to provide a satisfactory self-object environment.

Such failures transform the normal upsurge of affectionateness and assertiveness—essential attributes of the proud and joyful oedipal self—into the pathological and pathogenic drives, which we traditionally viewed as the manifestations of the final stage of normal infantile sexuality. As with “pre-oedipal” infantile sexuality and destructive aggression, we consider the infantile sexuality and hostile-destructive aggression of the oedipal phase (i.e. the Oedipus complex) to be disintegration products. As such, they supervene only after the selfobjects [usually the parents] have failed to respond to the primary affectionateness and assertiveness of the oedipal-phase self with fondness and pride because they [the parents] have, on the basis of their own psychopathology, experienced (preconsciously) these emotions of their oedipal child as sexually stimulating and aggressively threatening. (26, p. 390)

If, on the other hand, the parents are able to provide a good self-object milieu, the child is “able to assimilate the oedipal lesson, i.e., change his goals and with that his self-concept . . . [and he becomes] able to accept without a sense of permanent loss the fact that his selfobjects are selves in their own right and have needs that at any given time may disregard or even be in opposition to his own. . . . He may come to recognize and understand that the selfobject needs of others are as significant and as worthy of respect as are his own” (14, p. 27).

Many patients have experienced serious preoedipal self-object difficulties. They, too, must go through the oedipal phase, but they must do so insufficiently pre-

pared. Failure is virtually inevitable, and oedipal material will overlie—and perhaps mask—serious preoedipal pathology (19, 20). Clinically, we believe that this describes the majority of today's narcissistically vulnerable patients. For them "it is not the unconscious fear of forbidden erotic love that generates anxiety, but the anticipation of reexperiencing the devastating, potentially disintegrating disappointment of early empathic failures if they dare once again to reach for emotional fulfillment" (21). To try again, either in the outside world or in the therapeutic setting, to obtain in a later relationship what one did not get and needed as a child seems foolhardy on the one hand but essential for continued growth on the other.

TREATMENT CONSIDERATIONS

The self psychology literature grew out of classical psychoanalysis. However, its theory and practice can be directly applied to psychotherapy. From a self psychological perspective, there is a continuum from psychoanalysis, through psychoanalytically oriented psychotherapy, to focal therapy. The major difference is that "psychoanalysis places the transference neurosis into the center of the therapeutic activity, whereas psychoanalytic psychotherapy focuses upon intra- and *extratherapeutic* [italics added] transferences within the broader context of the therapist-patient relationship" (22). This continuum is valid so long as "the therapist's interventions are not manipulative (supportive [educative, advice giving] or reassuring) but, rather, are fairly consistently interpretive (23).

The primary content of self psychology's interpretive focus has shifted from unconscious conflicts and disavowed wishes. Instead, it focuses on how patients try to restore a sense of vitality, cohesion, or harmony to the self when it is 1) threatened by the disruption of an important self-object tie or 2) injured by some narcissistic assault. While symptomatic behavior has obviously negative elements and may express profound narcissistic rage, it is primarily understood as an attempt at restoration of a fragmenting or depressed self and therefore contains an important element of health. Symptoms are not primarily understood as efforts to seek symbolic gratification of unresolved conflicts. Interpretations focus on the nature of self-object disruptions and narcissistic insults, what the self experiences in the face of these, the rage that may be provoked, and what the patient does to restore to the threatened self a feeling of vitality. For example, with patients who shoplift, interpretations do not focus on symbolic gratification of object-instinctual drive conflicts. Rather, events in the patient's life that were experienced as disruptions of vital self-object ties or narcissistic assaults are sought. Then an attempt is made to understand how the symptoms restore the cohesion and harmony of the self, perhaps by reducing intolerable rage or by giving a sense of power (24).

The therapist serves as a self-object in the therapeutic

environment of sustained, empathic understanding. The goal here is to resume the thwarted developmental process, forming internal structures that assume the functions provided by self-objects. It is then possible for self-object relations to change from archaic to mature. To provide this necessary self-object environment, Kohut and his colleagues repeatedly stressed that it is both unnecessary and unwise to gratify any need of the patient other than the need to be accurately, empathically understood (4). Other needs are interpreted and related to genetic material.

While substantial empathic success is necessary to establish and maintain the self-object bond between patient and therapist, it is inevitable that the therapist will occasionally fail—content or timing of an interpretation will be wrong, vacations come at the worst possible time, and so on. These "failures" may be experienced by the patient as serious disruptions of the developmentally essential self-object tie to the therapist. Such disruptions must be acknowledged by the therapist, who must accept his or her contribution (however unintended or impossible to avoid). When the self-object bond is reestablished, the therapist may helpfully point out the origins of the patient's distress in the disappointments of childhood.

The disruption and reestablishment of the self-object bond engender both the necessity and the opportunity for patients to create or develop, through transmuting internalization, intrapsychic structures by which they may better internally regulate self-esteem, calm the self, and so on. This process occurs many times in the course of therapy—often with such fierce intensity that the therapist may fear the therapeutic alliance has been ruined. We cannot overemphasize that, if the bond is genuinely reestablished, the very intensity of the disruption indicates that the therapeutic process is working as it should.

Accepting the most trivial of a patient's demands as important may seem *prima facie* an unreasonable acceptance of the most irrational of the needs. What is meant, however, is empathically acknowledging how important the need is to a patient—not gratifying it, agreeing, or disagreeing with it. Any of those three responses (including correcting a patient's distortions) will risk interfering with, or even destroying, the vital self-object tie to the therapist. Furthermore, being understood results in a "consolidation of the self [which] appears to enable patients to experience and explore affects they could not tolerate previously, either because of their intensity or because of their particular content: jealousy, rivalry, hostility, love, sadness, guilt, shame" (23). Only after the self has been sufficiently consolidated through the sustenance of the self-object transference and interpretation of perceived self-object failures can patients begin to see how the urgent intensity or vulnerability they experience is a reaction based on early self-object failure. Often it is the patient who comes to this realization, obviating the need for the therapist to interpret the transference and other distortions.

Both object and self-object transferences are seen in all patients. The former include castration anxiety secondary to competitive feelings toward the therapist, and so forth. There are five primary self-object transferences: merger, contact shunning, mirroring, idealizing, and alter ego. One may see, for example, a patient who is attentive to the slightest nuances of our responses, reading them as fierce criticism or extravagant praise. The smallest perceived insult will result in a disruption in this mirror transference and may cause the patient to fly into a rage, collapse into depression, or indulge in acting out.

Kohut believed that patients with character and behavior disorders formed self-object transferences throughout most of their therapy but that they formed object transferences toward the end of treatment. With neurotic patients, the sequence is reversed. They are struggling primarily with the consequences of oedipal conflicts and have developed a reasonably secure nuclear self. As the neurotic conflicts resolve, these people discover underlying disappointment, grief, and rage that their parents were unable to sufficiently meet legitimate self-object needs during the oedipal period. These feelings are then worked out in the transference. Wolf (25) did not find such clear sequences of transferences in his patients. Rather, he considered that the transferences alternate throughout treatment, with self-object transferences clearly predominating in patients with character and behavior disorders. With neurotic patients, Terman acknowledged the obvious and important presence of conflicted object transferences. However, he cautioned, "with respect to technique, in patients with injury to the oedipal . . . self, attention must be directed to the parental responses—as perceived by the patient—and their role in the genesis of the injury. Attributing the self-injurious attitudes to the strength of underlying impulses re-creates the original narcissistic injury" (26).

We may summarize the therapeutic process using Wolf's guidelines (27). He described five steps in the analytic process, which apply directly to psychotherapy.

1. Analysis of defenses against therapy, the fears of further self-object failure, and the painful injury the failures inflict. Condition: ambience of acceptance and understanding, which is necessary for and encourages regression and mobilization of transference.

2. Unfolding of the self-object transference. Condition: noninterference with this process by judgmental interpretations, such as educative comments as to the nature of the patient's oversensitivity, what the boss really meant, and so forth.

3. Inevitable disruption of the sustaining self-object relationship. Condition: the failure to fulfill must be optimal.

4. Appropriate interpretation of the observed disruption, restoring mutual understanding by explanation. Condition: an honest and plausible explanation of the experienced disruption as blamelessly unintentional and probably unavoidable.

5. The patient's self, now strengthened, continues the deeper unfolding of more archaic self-object needs in the transference. The therapist then points out the patient's failures *and* successes in strengthening the self and attempting to integrate into the surround in a way that establishes healthy, mature (rather than archaic) self-object and object relationships.

Extended descriptions of self psychologically informed analysis have been offered by Kohut (28), Tolpin (29), and Goldberg (30).

CONCLUSIONS

We can perhaps best conclude by quoting Kohut. He was referring to analysis *per se*, but the comment also applies to effective psychotherapy in general.

A well-conducted analysis . . . which has been brought to a proper conclusion, provides the analysand with more than the diminution or disappearance of his painful and disturbing symptoms—existing in him now is a certain psychological openness, perhaps even a spark of that playful creativeness which turns toward new situations with joyful interest and responds to them with life-affirming initiative. Such a person may yet continue to be more easily traumatized than one who has learned to maintain a reliable yet restricting psychic equilibrium. But he will also be more perceptive and responsive than the rigidly normal. (31)

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The Discharged Psychiatric Patient: A Review of Social, Social-Psychological, and Psychiatric Correlates of Outcome

William R. Avison, Ph.D., and Kathy Nixon Speechley, M.A.

The authors review research over the past decade on the social, social-psychological, and psychiatric correlates of community adaptation among discharged psychiatric patients. A review of 33 studies suggests that little theoretical or methodological progress has been made in identifying the factors that are conducive to the adjustment of discharged patients on their return to the community. To stimulate subsequent efforts in this area, the authors suggest applying new approaches, such as the stress process perspective that has been used to study mental health in the general population.

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Over the last three decades, radical changes have occurred in the treatment of the mentally ill. One of the most important of these has been the shift in the locus of treatment from large public mental hospitals to community-based programs. Today, community care and the avoidance of lengthy hospitalization are common treatment policies. Now, hospitalization of the mentally ill is seldom measured in terms of years but is more often a matter of months or even weeks.

This shift in treatment philosophy has generated a large body of research that has examined the correlates of adaptation of the discharged patient to life in the community. The research can be divided into four categories: 1) research on the impact of inpatient treatment modalities on posthospital adjustment (1-3), 2) research on the effectiveness of community-based alternatives to hospital treatment (4), 3) research on the efficacy of community support systems in assisting the former inpatient to adapt to life in the

community (5), and 4) research that identifies social, social-psychological, and psychiatric correlates of successful community adjustment (6).

Most recent reviews of posthospital adjustment have focused on the first three categories. To the best of our knowledge, the latest review of social, social-psychological, and psychiatric correlates of outcome is that of Anthony et al. (2), who examined research published in the early 1970s.

Although it is clearly important to be informed about the kinds of programs that are effective in assisting former patients to adjust to the community, it seems equally important to know whether certain patients with particular characteristics are more likely to adapt to life in the community regardless of the kinds of treatment or aftercare they receive. There are at least two reasons for this. First, some proportion of discharged patients are lost to treatment because 1) hospital discharge rates have outstripped the capacity of community-based services (1), 2) there is little continuity in the services offered, or 3) some discharged patients choose not to use such services. Second, social and social-psychological correlates of community adjustment might suggest which discharged patients could be targeted for programs that have demonstrable efficacy. If community-based programs are unable to serve all discharged patients, then it would be useful to treatment and service providers to identify those individuals who are most at risk of maladjustment after discharge.

This review has two objectives. First, it summarizes the major findings of recent studies on community adjustment among discharged patients, most of whom have been diagnosed as psychotic. Second, it makes some theoretical and methodological suggestions that have potential for improving the quality of research in this field.

This article reviews follow-up studies that have identified factors associated with successful community outcomes for adults who have been discharged from full-time psychiatric facilities. Those studies that focused mainly on children, adolescents, the elderly, alcoholics, drug abusers, patients with organic disorders, or the mentally retarded have been excluded from consideration. This review is further restricted to studies whose main focus was on social, social-psychological, or psychiatric correlates of outcome. Studies that

Received July 25, 1985; revised Jan. 13, 1986; accepted Feb. 20, 1986. From the University of Western Ontario. Address correspondence to Dr. Avison, Health Care Research Unit, Kresge Bldg., University of Western Ontario, London, Ont., Canada N6A 5C1.

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focused primarily on the efficacy of treatment and service programs or interventions have not been included.

Social characteristics refer to demographic attributes, indicators of social class, and measures of previous employment history. Social-psychological variables include the extent and quality of social interaction with others, perceptions of self, and the experience of social support from others. Psychiatric characteristics refer to diagnostic and symptom ratings as well as to measures of previous hospitalization history.

The studies reviewed here were published between 1973 and 1984, inclusively. These studies were located by a computerized bibliographic search (Medical Literature Analysis and Retrieval System—MEDLARS), supplemented by an examination of the references in each article. This time period allows for an assessment of the literature on psychiatric outcome since the reviews of Anthony et al. (2) and Clum (6). Although it is unlikely that all studies in this period have been included, we believe that the present review of 33 studies is a broad one and is representative of outcome research over the last decade. (A tabular summary of the major characteristics of these studies is available on request.)

RESEARCH ON PSYCHIATRIC OUTCOME

An examination of these studies indicates that many different measures have been used to index the extent to which discharged patients adjust to their return to the community. Six different outcome criteria are the most commonly used:

1. Readmission during a specified follow-up period.
2. The proportion of time during the follow-up period that the patient spent in the community after the discharge of record or, alternatively, the proportion of time spent in rehospitalization.
3. Measures of the patient's core role performance as indexed by various employment indicators or, in the case of many women, their level of household performance.
4. Measures of social adjustment.
5. Measures of current level of symptoms at the time of interview.
6. Global ratings of outcome that represent combinations of some or all of these measures.

Readmission to the Hospital

Recidivism is by far the most prevalent measure of outcome used in the studies under review. Sixteen of the investigations meeting the criteria for this review evaluated patients' adjustment by using readmission to the hospital as an outcome measure (7–21; unpublished 1980 paper of Hermalin). Fifteen of these simply measured whether patients were readmitted during a specified follow-up period (8–21; unpublished 1980 paper of Hermalin). Caton (7) counted the number of readmissions during the follow-up time frame.

Five studies (7–11) found no differences between men and women in the likelihood of being rehospitalized. Only Byers et al. (12) and Miller and Willer (13) reported a statistically significant sex effect, but neither specified the nature of the relationship; however, Miller and Willer noted that the effect was extremely small. Given that the samples studied varied considerably in terms of diagnostic composition and length of follow-up period, it seems reasonable to conclude that sex differences do not importantly affect the likelihood of recidivism.

Few studies reported significant effects of race on readmission. Munley and Hyer (14) found that non-whites were somewhat more likely to be readmitted within 3 months of follow-up but observed no such differences at 1 year after discharge. Buell and Anthony (8) reported no significant differences by race, and Caton (7) found race to be unassociated with recidivism in a predominantly nonwhite sample of schizophrenic patients.

With regard to age, Di Scipio and Sommer (9), Fontana and Dowds (15), Lorei and Gurel (16), and Munley and Hyer (14) all reported no evidence of an association between age and readmission. In contrast, Christensen (17) noted that among a sample of schizophrenic men in Denmark, older patients were more likely to remain in the community following their discharge.

Earlier research tended to focus on the impact of education, marital status, living situation, social class, and posthospital employment. These studies argued that such social variables are indicators of what has been variously referred to as "social resources" or "social competence." Six investigations (8, 12, 14–16, 18) found education to be unrelated to readmission. Franklin et al. (19), Klein et al. (10), and Serban and Gidynski (18) found that married patients were less likely than single patients to be readmitted; Buell and Anthony (8), Christensen (17), Di Scipio and Sommer (9), and Lorei and Gurel (16) did not.

Buell and Anthony (8), Byers et al. (12), Caton (7), and Christensen (17) argued that social class has no effect on recidivism, but Serban and Gidynski (18) found that lower-class patients were more likely to be rehospitalized, and Munley and Hyer (14) reported a positive correlation between social class and readmission. Four studies (8, 14–16) found employment history to be unrelated to readmission. In terms of more recent employment history, Christensen (17) and Serban and Gidynski (18) reported that the employed were less likely to be rehospitalized. Similarly, Franklin et al. (19) and Klein et al. (10) reported that wage earners and individuals with higher incomes had lower probabilities of recidivism.

Zigler and Phillips (22–24) have developed an index that combines age, intelligence, education, employment, and marital status to generate a measure of social competence. Two studies reviewed here (15, 18) used variations on this technique to assess the relationship between social competence and readmission to the

hospital. Serban and Gidynski (18) combined patients' education, employment status, occupational level, and marital status; they found that the likelihood of readmission was negatively correlated with social competence for patients with chronic but not for those with acute schizophrenia. They noted, however, that patients with chronic schizophrenia who had low social competence scores were most likely to be rehospitalized but that patients with acute schizophrenia and moderate scores had the highest readmission rates.

Fontana and Dowds (15) combined age, marital status, occupational level, age at first hospitalization, number of years at current job, and number of months in current living situation to index what they called "social stability." They found no significant correlation between social stability and readmission over a 6-month or a 1-year follow-up period. It may be that the differences between their findings and those of Serban and Gidynski are attributable to variations in the dimensions included in the indexes and to the inclusion of both psychotic and nonpsychotic patients in the sample of Fontana and Dowds.

Among the studies that examined social-psychological correlates of recidivism, the main focus was on the impact of social interaction on readmission. Several investigations (10, 11, 13, 19) noted that rehospitalization was less likely among those individuals who were more involved in leisure activities. Other studies (7, 11, 19) reported that those who were in more frequent contact with friends and relatives were more successful in staying out of the hospital. Another body of research assessed the quality of social interaction as opposed to frequency of social contacts. Caton (7), Franklin et al. (19), Miller and Willer (13), and Willer and Biggin (11) all presented evidence suggesting that interpersonal conflicts in the home were associated with readmission. Klein et al. (10) also reported that individuals whose relatives had high expectations of them in terms of socially desirable behavior were less likely to be rehospitalized. The exceptions to these observations are Fontana and Dowds's report (15) that neither social involvement nor organizational participation was correlated with readmission and Christensen's finding (17) that social isolates were somewhat less likely to be rehospitalized.

Other researchers have argued that the importance for mental health of social interaction is manifested in the extent to which individuals experience social support from those around them (25, 26). However, little research has explicitly explored the role of social support in the community adaptation of discharged psychiatric patients. In the studies of recidivism that we reviewed, only Hermalin's unpublished 1980 paper investigated the effect of social support, finding that perceived level of support and public esteem were negatively correlated with recidivism.

The majority of the studies we reviewed attempted to predict rehospitalization on the basis of a range of psychiatric factors. There was widespread agreement that the number of previous hospitalizations for psy-

chiatric reasons was positively correlated with readmission (8, 9, 13, 14, 16, 17, 20). Only Byers et al. (12) and Willer and Biggin (11) found no association between these two variables.

Four studies (8, 15, 17, 18) suggested that the likelihood of readmission was higher for the more chronically ill psychiatric patient. Not surprisingly, measures of level of symptoms or psychopathology have also been reported to be significantly associated with recidivism (10, 15, 21).

What is somewhat surprising, however, is that so many of these studies failed to report whether diagnostic differences affected the probability of being rehospitalized. Only Buell and Anthony (8) indicated that schizophrenic patients were more likely to be readmitted to the hospital, but they found this relationship to be statistically nonsignificant.

The theme that emerges from a consideration of psychiatric correlates of recidivism is not a new one. As with earlier research (2), there is still good reason to believe that a patient's hospitalization history is a predictor of his or her ability to remain in the community. Although psychiatric variables are good prognostic indicators of readmission to the hospital, they do not advance our understanding of the process of community adaptation. Any attempt to develop a more comprehensive explanation of psychiatric recidivism may benefit from an approach that examines social and social-psychological factors while controlling for previous hospitalization history, current level of symptoms, or any other psychiatric variables thought to be importantly associated with the probability of readmission.

Community Tenure

Community tenure was used as an indicator of posthospital adjustment in only five (12, 27-30) of the 33 studies reviewed. Four studies (12, 27-29) used indicators of time spent in the community from the discharge of record to readmission or to the end of a specified follow-up period. Turner and Gartrell (30) calculated the percentage of time of the follow-up in rehospitalization; functionally, this measure is the reciprocal of time spent in the community.

These studies provided limited information on the social correlates of community tenure. Byers et al. (12) reported no age, sex, marital status, or education differences in the number of days spent in the community. Turner and Gartrell (30) also reported no association between age or marital status and percentage of time spent in the hospital in a sample of white male schizophrenic patients.

Earlier research on the community tenure of discharged psychiatric patients has documented the inverse correlation of social class and community tenure; only three studies reviewed here reported on this correlation. Turner and Gartrell (30) found that lower-class patients spent a greater percentage of time in the hospital after their discharge of record, but Byers et al.

(12) found no association between class and community tenure. One source of these differences may be that Turner and Gartrell's sample consisted solely of male schizophrenic patients, while the sample studied by Byers et al. included men and women with a variety of diagnoses. Earlier research has suggested that the association between class and posthospital adjustment is stronger for schizophrenic patients.

Three studies (28–30) converged in their findings concerning the correlation between employment and community tenure. Strauss and Carpenter (28, 29) found that duration of hospitalization was negatively associated with the amount of useful employment in terms of both duration and quality of work. However, they noted that prehospital employment was not associated with community tenure. In a similar vein, Turner and Gartrell (30) reported a significant inverse relationship between persistence of employment and time spent in the hospital.

Turner and Gartrell's study is distinctive among those that investigated community tenure because it addressed an interesting theoretical concern. They presented evidence that social class and work performance were both associated with community tenure even when age, marital status, education, severity of pathology, and class of origin were held constant. They argued that these associations may be interpreted in terms of *social competence*, as measured by intergenerational occupational mobility independent of education and class of origin. When time spent in the hospital was regressed on social competence, severity of pathology, age, marital status, and work performance, only the first two variables proved to be significant. Turner and Gartrell argued that these findings suggest that there is nothing intrinsic to marriage, higher social class, or working that directly affects community tenure. They asserted that "these relationships appear to arise as a consequence of conditions within individuals that are describable in terms of variations in psychopathology on the one hand and capacity for socially effective behavior on the other" (p. 378).

None of the five studies of community tenure examined the effect of social-psychological factors. Rather, the major focus of some of these studies was on the association between a range of psychiatric variables and outcome. Growe et al. (27) assessed the prognostic power of Hogarty and Ulrich's Discharge Readiness Inventory (31). This scale is composed of four subdimensions: community adjustment potential, psychosocial adequacy, belligerence, and manifest psychopathology. Growe et al. (27) reported that patients exhibiting more hostile behavior before discharge had shorter durations of stay in the community. Similarly, Turner and Gartrell (30) reported a negative association between psychopathology and outcome.

Three studies examined the relationship between hospitalization history and community tenure (12, 28, 29). Strauss and Carpenter (28, 29) found that the length of last hospitalization was negatively correlated

with time spent in the community, but Byers et al. (12) indicated that neither length of most recent hospitalization nor total time of previous hospitalization was correlated with community tenure.

It is essentially impossible to draw any general conclusions about the correlates of community tenure. Few studies investigated the issue; seldom were there common predictor variables assessed, and, where there were, the results of these studies were often contradictory.

Core Role Performance

Eight of the 33 investigations reviewed here examined factors associated with core role performance (8, 16, 21, 28, 29, 32–34). Role performance for men has traditionally been measured by employment and work history indicators. This has involved measures such as the number of weeks of work since discharge, employment status at follow-up, and the percentage of time employed since discharge.

The evaluation of core role performance among women is more difficult because some proportion of women choose not to work for a variety of reasons. In most studies, some decision has to be made about the assessment of core role performance among women in the home. Of the eight studies that reported on correlates of core role performance, seven included men and women (8, 21, 28, 29, 32–34); five of these evaluated housewives' role performance by how well the house was maintained and how well the children were cared for (28, 29, 32–34).

The primary focus of these studies was on social correlates. The most common finding was that the best predictor of economic performance after discharge was previous employment history (8, 16, 28, 29, 32). Age was negatively associated in the three studies where the relationship was tested (16, 32, 33), and Bland et al. (32, 33) found that patients who were married had better work histories following discharge.

Research on the social-psychological correlates of role performance is essentially nonexistent. Only Strauss and Carpenter (29) reported that patients' previous social contacts (as rated by significant others) were significantly associated with work performance.

Although a large body of earlier research documented the association between role performance and psychiatric variables such as diagnosis, symptoms, and hospitalization history, more recent research efforts have largely ignored these issues. Buell and Anthony (8) found that schizophrenic patients were less likely to be employed than those with other diagnoses. Strauss and Carpenter (28, 29) noted that length of previous hospitalization was negatively correlated with percentage of time employed 2 years after discharge but was uncorrelated with employment 5 years after discharge. Bland and Orn (34) reported that patients' presenting symptoms were associated with role performance as long as 14 years after discharge. Tessler and Manderscheid (21) noted that chronic medical prob-

lems negatively influenced job performance but indicated that behavioral problems did not have any substantial impact on work.

Social Adjustment

Only seven studies have examined some dimension of social adjustment (7, 21, 28, 29, 32–34). All of these considered social adaptation in terms of the quantity and quality of interaction with other people. Although there seems to be some agreement about the nature of this variable, its correlates have not been systematically examined.

Only one group of researchers (32, 33) has studied any demographic characteristics of discharged patients that might be associated with social adaptation. This group found no sex differences in adjustment but reported that younger discharged patients and those who were married were better adjusted socially.

Beyond these demographic variables, there is some evidence linking social adjustment to both basic life skills and work history. Tessler and Manderscheid (21) noted that skills for community living such as maintaining personal hygiene and managing money were associated with greater social activity after discharge. A good premorbid work history was found to be correlated with social adjustment by Bland et al. (32) but was reported by Strauss and Carpenter (29) to be unrelated to social adjustment.

Only one social-psychological variable, social interaction, has been studied in relationship to social adjustment. Strauss and Carpenter (28, 29) indicated that premorbid social relationships were associated with both the quantity and quality of posthospital relationships. Once again, we note that the best predictor of future behavior is past behavior.

Psychiatric variables have frequently been the subject of interest with regard to social adjustment. Strauss and Carpenter (28, 29) noted that length of previous hospitalization was negatively related to social adjustment in a 2-year follow-up, but they reported this same correlation to be nonsignificant in their 5-year follow-up of the same sample. Caton (7) also reported no significant correlation between length of inpatient stay and social functioning, but Bland et al. (33) indicated that social outcome was negatively related to length of hospitalization at first psychiatric admission.

Bland et al. (32) examined the relationship between social adjustment and symptoms. Not surprisingly, they found that indications of confusion and guilt were negatively associated with social adjustment. In a subsequent study, Bland and Orn (34) reported that symptoms at first admission were negatively correlated with social adjustment 14 years later.

To this point, available research presents no comprehensive picture of the factors associated with the social adjustment of discharged psychiatric patients. The information that is available is somewhat fragmented, suggesting the absence of any systematic re-

search strategy. Furthermore, some findings appear to be somewhat tautological; to suggest that some individuals who exhibit symptomatic behaviors are likely to have problems in social adjustment does not fundamentally improve our understanding of the factors that contribute to adaptation.

Current Level of Symptoms

Twelve studies provided few insights into the factors associated with symptomatic behavior among discharged patients (7, 28, 29, 32–40). Vaughn and Leff (35, 36) reported that men were more likely to exhibit higher levels of symptoms at follow-up. Bland et al. (33, 34) noted that both age at first admission and marital status at follow-up were associated with fewer psychiatric symptoms at follow-up. Sartorius et al. (37) and Vaughn and Leff (35) found a similar correlation with marital status. Bland et al. (32) also indicated that premorbid work history was associated with less symptomatic behavior; however, Strauss and Carpenter (29) failed to find such a correlation in their study. Other than these investigations, we found no research examining the effects of social factors on level of symptoms.

Some attempts have been made to examine the role of social-psychological processes on level of symptoms. Strauss and Carpenter (29) observed that the level of social contacts before initial evaluation was a significant predictor of symptoms at follow-up, and Sartorius et al. (37) noted that social isolation was associated with symptomatic behavior.

Vaughn, Leff, and their colleagues (35, 36, 38, 39) have made an important contribution to our understanding of the ways in which patients' interactions with their family members affect the course of schizophrenia. Their work has focused on the concept of expressed emotion, the tendency for family members to be critical of the patient, hostile, and emotionally overinvolved. In their initial study, Vaughn and Leff (35) reported significantly higher rates of recurrence of symptoms over a 9-month period among patients whose family members exhibited high scores on measures of expressed emotion. This correlation persisted when patients were followed for 2 years (39). These British studies were replicated in an investigation of schizophrenic patients in southern California (39). In addition, Leff and Vaughn (38) elaborated on the findings, noting that the reappearance of schizophrenic symptoms was associated with either high expressed emotion or with an independent life event. Taken together, this body of evidence represents a major contribution to this field of study insofar as it stresses the dynamics of family relations in the course of psychiatric illness.

Information on psychiatric correlates of symptomatic behavior is also sparse. Although Strauss and Carpenter (28, 29) noted that the duration of previous hospitalization was associated with symptoms at follow-up, Caton (7) reported that length of last hospi-

talization was unrelated to level of symptoms. Clum (40) noted a significant association between symptoms at baseline and those observable at follow-up, controlling for a variety of other social, social-psychological, and psychiatric variables.

Global Ratings of Outcome

In recent years, there have been some attempts to assess psychiatric outcome by global ratings that use some combination of outcome measures discussed thus far. Our review identified eight such attempts (28, 29, 32, 34, 41–44). Bland et al. (32, 34) developed a 10-point measure that takes into account psychiatric condition, social adjustment, and economic productivity. Grob et al. (41) used a two-factor measure that includes indicators of level of functioning/improvement and measures of helpfulness/satisfaction. Hawk et al. (42) used the sum of nine outcome scores including work function, quantity and quality of social relationships, severity of symptoms, and fullness of life. Strauss and Carpenter (28, 29) combined measures of employment record, symptoms, social contacts, and time spent out of the hospital. Moller et al. (43) employed the Global Assessment Scale (45), a measure of global level of functioning that takes into account psychopathology, interpersonal relations, and work. Vaillant (44) used a measure defined by five criteria including dimensions of symptoms, adjustment, prescribed drug use, and maintenance of interpersonal relationships.

Despite these attempts to develop global assessments, the search for correlates has been limited and contradictory results have emerged. Bland et al. (32) found a negative correlation between age and outcome, but Grob et al. (41) and Moller et al. (43) found a positive association. Bland et al. (32) and Vaillant (44) observed that married individuals scored higher on global measures of adjustment than did the unmarried. No other studies have evaluated the impact of sociodemographic factors on global outcome.

Discrepancies in results concerning the correlation between work history and global ratings of adjustment draw attention to a problem with such measures. Bland et al. (32) and Moller et al. (43) found a significant correlation between a good work history and global outcome, but Strauss and Carpenter (29) found the correlation to be nonsignificant. In part, these differences appear to be due to the fact that Bland et al. included an indicator of economic productivity as one of three components of their global measure, while only two of nine indicators on Strauss and Carpenter's global measure are related to employment. Given that the measure devised by Bland et al. assigns greater weight to economic productivity than does the index devised by Strauss and Carpenter, it is not surprising that work history would be a better predictor of the outcome measure in the Bland study.

The only social-psychological correlate that has been examined in relation to global outcome is social

interaction. Strauss and Carpenter (29) indicated that those discharged patients who were more involved in interaction with others scored higher on global outcome measures.

The impact of patients' psychiatric characteristics on adjustment has been investigated in seven of the studies we reviewed (28, 29, 32, 34, 41–43). Hawk et al. (42) and Moller et al. (43) reported that nonschizophrenic patients had significantly better outcomes than schizophrenic patients. Grob et al. (41) noted that patients with affective psychoses had better outcome scores than those with schizophrenia or those with personality disorders. Other studies (28, 29, 32, 43) converged in reporting that length of hospitalization was negatively associated with global outcome. Only Grob et al. (41) found no association between hospitalization history and outcome; however, their outcome measure is considerably different from those employed in other studies. It measures patients' self-reports of improvements in their level of functioning. Bland et al. (32) reported a weak negative correlation between one dimension of symptoms—confusion—and outcome. In a subsequent study, Bland and Orn (34) noted that frequency of symptoms at first admission was negatively associated with outcome 14 years later.

It is difficult to evaluate the results of studies that use different measures of global outcome. It seems clear that these various scales differentially emphasize selected facets of outcome. Although some appear to stress work performance, others emphasize symptomatic behavior; still others have a strong social interaction component. At the very least, caution must be advised with regard to the comparability of global outcome measures.

DISCUSSION

In their earlier review, Anthony et al. (2) noted that recidivism and employment were the most frequently used indicators of outcome. They concluded that the strongest predictor of recidivism was previous hospitalization, while previous employment was the best predictor of employment. They also argued that social and work-related skills were better predictors than diagnostic labels or symptoms. This conclusion is not fully supported by our review. Although there is evidence that social, interpersonal, and work skills are good predictors of outcome, psychiatric variables also predict these outcomes. The nature of most studies included in this review makes it impossible to compare the predictive power of these variables. More recent research on the correlates of psychiatric outcome appears to reflect a continuation of previous trends in the area. The vast majority of studies have measured outcome by hospitalization experience, community tenure, or employment after the discharge of record. Although these data can be obtained with relative ease, their validity is clearly at issue. Anthony et al. (2) also

advocated the development of additional indicators of outcome. Very few studies have addressed this problem or attempted to assess patients' adjustment in the community by using indicators of role performance, social adjustment, or other measures of this kind. Thus, little progress has been made toward the development of valid and sensitive measures of adjustment. This is not to imply that measures of recidivism and community tenure are of no value. Rather, we suggest (as did Anthony et al.) that these traditional indicators may be usefully supplemented by indexes which assess other dimensions of community adjustment.

A similar conclusion seems warranted when one considers the factors that have been studied in relation to these flawed measures of outcome. As with previous work in this area, more recent studies tend to focus predominantly on social and psychiatric variables that are associated with lower probabilities of readmission to hospital. In general, these studies fail to advance our understanding of the process of adjustment. Rather, they simply identify broad categories of patients who are at risk of subsequent rehospitalization. In many respects, these studies, conducted over the last 10 years, largely confirm the relationships uncovered more than two decades ago. In this sense, recent work basically represents a continuation of previous lines of inquiry, complete with attendant theoretical and methodological shortcomings: poor conceptualizations, small and heterogeneous samples that prohibit powerful statistical analyses, imprecise measures of predictor and outcome variables, and few attempts to examine the possibilities of statistical interactions. (Space limitations prohibit elaboration of these problems; a discussion of these issues is available on request.) In short, there is a pressing need for new approaches to the area.

It is apparent that most research on the adjustment of discharged psychiatric patients lacks theoretical direction. It can be argued that this problem stems from researchers' difficulties in clearly articulating the meaning and measurement of adjustment. This task is difficult because these terms are likely to mean different things to different people. The issue, therefore, is one of normative theory (46), depending largely on values about which universal agreement is unlikely. If, as we believe, any definition of adaptation involves value choices, it may be possible for researchers to specify their normative assumptions about adjustment among discharged psychiatric patients.

There appear to be at least five normative value assumptions that may be operative in this area (R. Jay Turner, personal communication). These assumptions are that it is better for discharged psychiatric patients 1) to be in the community than to be hospitalized, 2) to be productive and active than to be idle, 3) to be involved with others in social relationships than to be isolated, 4) to be able to cope with the stresses of daily living than to be distressed by them, and 5) to conform to the behavioral and role performance expectations of significant others than not to conform.

The specification of these normative assumptions

has three advantages for researchers. First, each suggests a dimension of adaptation that can be operationally defined. Second, it draws attention to the idea that community adaptation is a multidimensional construct. Such a recognition should stimulate efforts toward the refinement and increased use of more comprehensive instruments of the type developed by Ellsworth (47) and Endicott et al. (45). A third advantage becomes apparent if one considers the normative assumptions that we have enumerated. The various dimensions of adjustment implied by these normative judgments constitute benchmarks by which we measure the mental health of the general population. The observation that these assumptions are not restricted to people who have been hospitalized because of mental illness also suggests that theoretical models of psychological distress in the general population might be of use in studying adjustment among discharged patients.

For example, there is a growing body of literature on the study of the relationship between stressful life events and psychological distress (48–50). Attention has been given to the importance of identifying the process that is formed by the interconnections of the separate components of stress. The stress process, as conceived by Pearlin et al. (51–53), involves a complexity of relationships among life events, chronic life strains, mediating resources, and the outcome of stress. The importance of considering factors that may act as amplifiers as well as those that may buffer the impact of stress has been voiced by those studying the process (53, 54). The role that chronic strain plays in amplifying the stress process has also been examined (51, 55), and social support and coping resources have been shown to moderate the relationship between life stress and psychological distress (52–54). There is also evidence to suggest that social support has a direct effect on psychological health among diverse populations (56, 57).

There are at least four reasons why this conceptualization of the stress process may be important to those who are interested in research on psychiatric outcome. First, this body of knowledge enables us to conceive of posthospital adjustment as a dynamic interaction among the discharged patient, other people, and the environment. Such a model introduces an important social-psychological dimension into a consideration of the process of adjustment. Second, measures of the various components of the stress process have been developed that have satisfactory formal properties and that could easily be introduced into investigations of community adjustment (48, 50, 52, 53, 56–58). Third, this body of research suggests viable hypotheses that might stimulate further research on correlates of adjustment. Fourth, because theoretical perspectives on the stress process conceive it to be dynamic and ongoing, research strategies that use longitudinal designs have been generated. If community adjustment is viewed as a process rather than as a static outcome, psychiatric follow-up studies will do well to adopt

longitudinal strategies. Such approaches have the advantage of allowing for the study of change over time as well as providing a stronger basis for making causal inferences.

CONCLUSIONS

Over the last 10 years, research on the social, social-psychological, and psychiatric factors associated with community adjustment among discharged psychiatric patients has made few theoretical or methodological advances over earlier work in this area. The search for correlates of successful adaptation to life in the community appears to be stalled; most studies replicate findings reported in earlier decades.

We suggest that this lack of progress may stem from the absence of a theoretical perspective that could stimulate research into the process of community adaptation. One potential approach is the application of the stress process perspective that has been used to study mental health in the general population. This approach brings with it a rich source of research hypotheses, a pool of research instruments with good measurement properties, and a method that encourages the development of longitudinal research designs. If future research is to make any advance over the work of the last decades, the application of new theoretical and methodological approaches to the study of psychiatric outcome seems warranted.

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Experiential Sampling in the Study of Multiple Personality Disorder

Richard J. Loewenstein, M.D., Jean Hamilton, M.D., Sheryle Alagna, Ph.D.,
Nancy Reid, R.N., M.S.N., and Marten deVries, M.D.

The authors describe the application of experiential sampling, a new time-sampling method, to the assessment of rapid state changes in a woman with multiple personality disorder. She was signaled at random intervals during study periods and asked to provide information on alternate personality switches, amnesia, and mood state. The alternates displayed some characteristics that were as different as those occurring between separate individuals studied previously with this method. There were notable discrepancies between the self-report study data and information reported during therapy hours. The authors conclude that the phenomenology of multiple personality disorder is frequently more complex than is suspected early in the course of treatment.

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Despite the classic single case studies of multiple personality disorder by Ludwig et al. (1) and Larmore et al. (2) and more recent descriptive and psychophysiological studies of larger series of multiple

personality patients (3-9), much of the literature on the disorder consists of partial, single clinical case reports from which sweeping conclusions are drawn.

We describe the application of experiential sampling, a new behavioral time-sampling method, to the assessment of rapid mood, self-perceptual, and clinical state changes in a woman with multiple personality disorder. The purpose of the study was to examine the utility of experiential sampling in the study of a clinical syndrome characterized by frequent, rapid state changes (switching of multiple personality alternates) that were readily apparent to the treating psychiatric staff but were of uncertain periodicity in nonclinical, everyday situations. We also wished to make a contribution to the systematic study of the phenomenology of multiple personality disorder.

Experiential sampling permits comparison of a naturalistically derived sample of the patient's own experience with clinical observations, standardized single-time-of-day rating instruments, and psychophysiological and other laboratory measures. Subjects collect data about their own experience at different times during the day. Experiential sampling can help characterize clinically significant, within-day variations in mood, behavior, and experience such as the immediate precipitants of switch processes or mood changes. It helps minimize the biases that may occur with single-time-of-day reports based on retrospective, global recall of symptoms or precipitants of symptoms (10). Experiential sampling has been used in the study of normal subjects, schizophrenic patients, and patients with eating disorders, but the range of its applications to clinical psychiatric research has not been fully explored (10-14).

In this report we will use the relatively neutral terms "alter" and "alternate" whenever possible instead of "personality." We know of no well-accepted rigorous definition of the term "personality" in the literature.

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These data were collected with Dr. Hamilton as principal investigator under her protocol NIH 81-M-11, based on her previous experience with this sampling method; and with Dr. Loewenstein as the primary clinician and co-investigator.

TABLE 1. Characteristics of the Main Alternates of a Woman With Multiple Personality Disorder Studied With the Experiential Sampling Method

Name	Current Age	Sex	Reported Basic Affects, Purpose, and Characteristics	Reported Additional Characteristics	Reported Age When Fully in Existence	Stated Precipitant of Creation ^a	Identifications or Shaping Factors	Amnesia Score ^b
Jennifer Sue	Early 30s	Female	"Host personality" (8); fearful, depressed, amnesic	Sexuality, motherhood	"There since the beginning"		Attempted to follow manifest conventions of family of origin	4+
Jennifer	Early 30s	Female	An organizer; rational, orderly, cognitively oriented, little overt affect	College degree in social science	7 years	Verbal and physical abuse by mother, responded by not showing feelings	Intellectual interests	1+–2+
Taylor	Adult (20s)	Neuter to female	A protector; independent, aggressive, joking, pacing	Interested in cars, athletics; has mechanical aptitudes not shared by others	9 years ^c	"Unfair" discipline by a teacher in school, punched the teacher	Identification with grandfather; "maybe what they really want is a boy"	2+
Regulator	Adult	Neuter to male	"Memory trace personality" (8) (i.e., denies amnesia); "control of others' access to time"; little physical ability	The internalized "voice of the father"; seen as very punitive; demands suicide by the others or punishes them for indiscretions	About 5–6 years	Being beaten by father, terrified of attacks at home	Identification with/introjection of aggressor; "if we took the father inside, we thought maybe we could control him . . . , but it didn't work"	0

^aOften alternates are described as "existing" before fully coming into being.

^b4=severe, 0=none.

^cMay have existed at a younger age but with similar characteristics.

We feel that it is more important to characterize the variety of discrete behavioral states seen in multiple personality disorder without prematurely implying that they conform to a particular form of superordinate psychological organization.

METHOD

The Patient

Ms. A, a white woman in her thirties, had a childhood history of severe physical, sexual, and emotional abuse and met all three *DSM-III* criteria for multiple personality disorder. Her initial clinical presentation has been described in detail in a prior communication (15). She was admitted to the National Institute of Mental Health (NIMH) inpatient service on an emergency basis because of suicidal ideas and mood swings. She initially received a diagnosis of rapid-cycling or mixed-state bipolar illness and was treated with lithium and fluphenazine, with little response. Subsequently, the treating psychiatrist (R.J.L.) identified five separate alters with different names and stated ages, mannerisms, styles of dress, postures, dominant moods and/or activity states, and vocal and cognitive styles. It became clear that the apparent rapid-cycling observed on admission had been a manifestation of rapid switching of alternates. Over the next 6 months, 16 addi-

tional alters were described. Characteristics of and pseudonyms for the main alternates described in this study are presented in table 1. The patient gave oral and written informed consent for research participation and publication of her history. All names and demographic data pertaining to the patient have been altered to preserve anonymity.

Procedure

The patient was studied in two 3-day periods during the first and third weeks of the final month of her 3-month NIMH inpatient stay. During the study the patient was free to enter and leave the hospital on her own schedule and had visitors. Between 8:00 a.m. and 11:00 p.m. during each study period, an electronic beeper was used to signal the subject to fill out self-reports according to a preselected, randomized time schedule generated by a random-number table. Each rating form asked for the following information: 1) time of day; 2) "who was 'out,'" referring to the alternate "in control of the body" before the beep; 3) whether a switch had occurred or whether time had been "lost" (psychogenic amnesia experienced) since the last signal; 4) contextual information such as where she was, whom she was with, and what she was doing; 5) motivational information such as why she was doing what she was doing and her wish to be doing something else, measured on a 10-point scale; 6)

responses to 13 dichotomized mood adjectives on a 7-point scale; 7) global reports of physical symptoms; and 8) the main global mood or feeling state as she was beeped. The reliability and validity of the method have been detailed elsewhere (10).

During each study period a number of data were collected. The treating physician and a second rater (N.R.) made separate blind predictions of the percentage of time each alter would be out during an average day and the proportion of time—from high to low—that an alter would tend to be out. In addition, blind predictions were made about the different alternates' responses to the mood and motivational scales. The raters also developed brief global descriptions of each alter. Data were also collected about the switch process itself. All reports of switches were mapped according to the time of day and who was out before and after. Switches were examined to see if any kinds of situations and mood or feeling states were related to the frequency of switching or to the emergence of specific alters.

We gathered qualitative data by examining the handwriting style and other idiosyncratic features that characterized the self-report forms completed by the different alternates. Experiential sampling data were also compared with clinical observations from individual and group psychotherapy and from the hospital milieu.

RESULTS

There were 21 responses to 24 signals in the first study period and 10 responses to 16 signals in the second. Although 21 alternates had been identified clinically, only seven ever responded to the beeper signal, alone or in combination. The latter was subjectively experienced as either a transitional state in which one alter was departing while another took over or as several alternates out together. Only four alternates—Jennifer Sue, Jennifer, Taylor, and the Regulator—responded more than once (table 1). In the first study period Jennifer Sue responded 33.3% of the time; Taylor, 25%; the Regulator, 16.7%; and Jennifer, 12.5%. This frequency was significantly correlated with that predicted by the therapist ($r=.78$, $df=4$, $p<.05$), and there was a similar trend in the ratings of the second observer ($r=.78$, $df=4$, $p<.10$). In the second study period only three alternates responded: Jennifer Sue answered 80% of the beeps, and Jennifer and Taylor responded to the others. On the basis of reports of who was out before and after a signal, we concluded that the beeper itself did not usually provoke a switch. On the basis of reports of amnesia and switching between the signals, we extrapolated that Jennifer Sue not only responded most often but was also out the longest total time of all alternates during both study periods.

Because multiple personality disorder is characterized by complex psychogenic amnesia, there may be

"amnesia for amnesia" and alters may underreport switching (8). We attempted to cross-check for this by discussing with several alters on each study day whether additional amnesia had occurred but had not been reported. Although we cannot exclude this possibility, all alters vehemently insisted that the ratings were completed accurately.

In general, the alternates were cooperative in filling out the study materials. The exception was the Regulator, who was viewed by both raters as the least likely to cooperate with the study. This prediction was confirmed: the Regulator did not complete any of the ratings aside from self-identification.

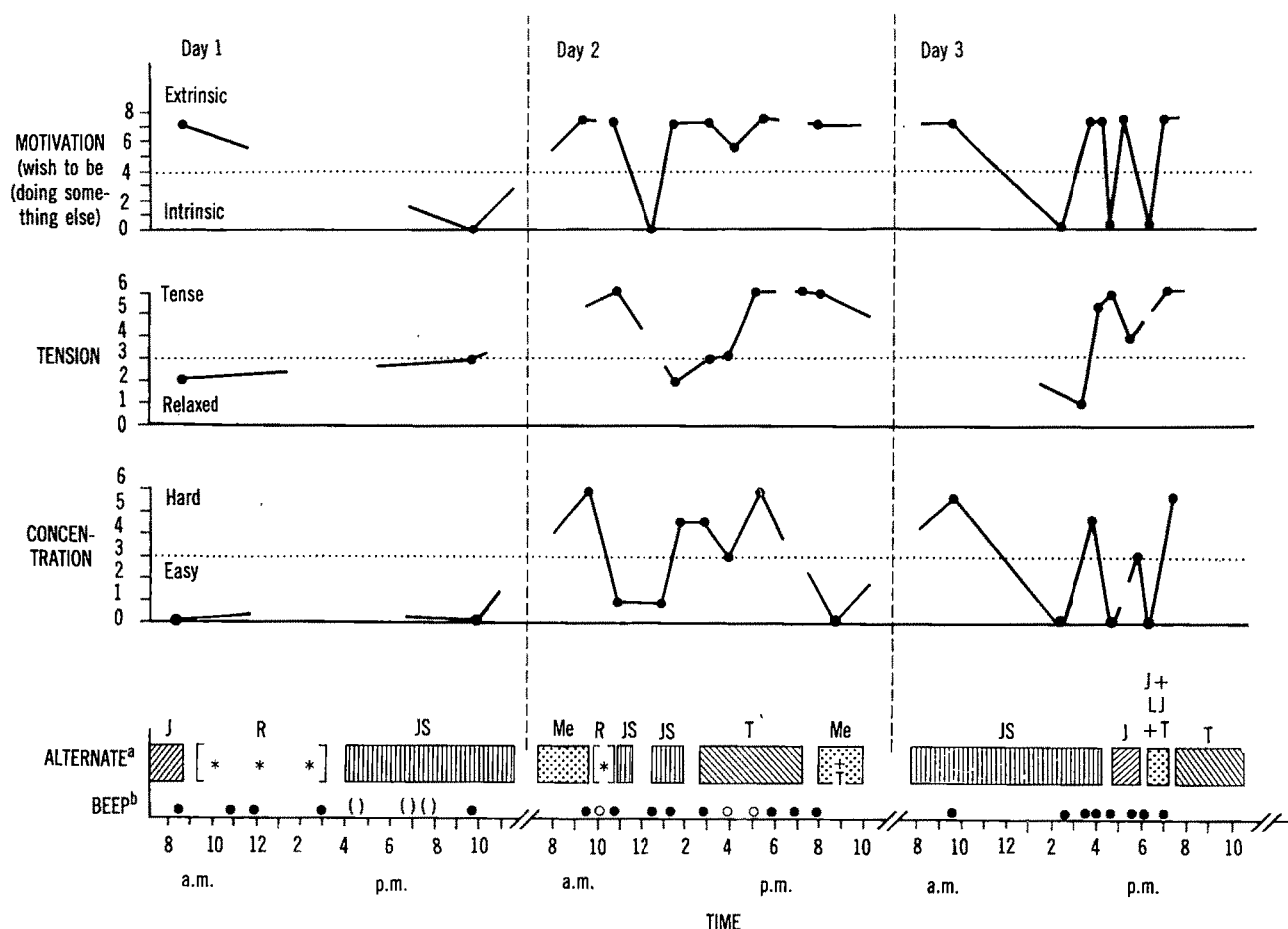
During the first study period there were 11 switches reported between 24 beeper signals (range=3–5 per day). There were only three switches reported for the second condition (range=0–2 per day). Forty-three percent of all switching occurred in the morning, and 47% occurred in the afternoon and evening. Switches were reported between nighttime sleep and waking beeps, although no changes were reported after an afternoon nap. On three occasions during the first study period (figure 1, day 2, open circles) additional ratings were completed, apparently owing to malfunction of the beeper. Data collected at these points were completely consistent with those generated at other times during the study. Figure 1 shows a graphic representation of the alternates' responses to the beeper signals, as well as their responses to several of the self-report items.

Examination of the actual rating forms revealed striking differences in how the forms were used by the different alternates. Some showed little variability in marking scale items, whereas others consistently rated themselves at the extremes. For example, Jennifer Sue mainly used the 0 or 5 rating on the 7-point scale but left other items blank. Jennifer used the 3, 0, and 6, while Taylor preferred the 3 and 4 but used the entire range of the scale, leaving a different set of items blank. One alternate usually circled the items, while another characteristically marked through them. These characteristics remained quite constant among the responding alternates.

Mood states were examined on the basis of the rating scale data for the three alternates who responded completely and often enough for analysis. Analysis of variance showed a significant difference on "weak-strong" mood ratings among alternates, with Jennifer feeling the strongest (mean \pm SD score = 6.0 ± 0), Taylor the weakest (score = 1.5 ± 1.7), and Jennifer Sue in between (score = 4.6 ± 2.3) ($F=3.62$, $df=2,17$, $p<.05$). There was also a nonsignificant trend among the alternates in the "hard to concentrate" and "alert-drowsy" ratings, with Taylor being the most different from the other two. Her respective scores were 5.5 ± 1.9 and 3.0 ± 0 , compared with Jennifer Sue's scores of 3.9 ± 3.1 and 4.9 ± 1.4 and Jennifer's scores of 1.0 ± 1.7 and 6.0 ± 0 .

Prior research on experiential sampling has documented a within-person correlation between mood and

FIGURE 1. Self-Ratings of Alternates of a Woman With Multiple Personality Disorder in Response to Randomly Timed Electronic Beeps



^aJ=Jennifer; JS=Jennifer Sue; T=Taylor; R=Regulator; LJ=Little Jenny, a child alternate; and Me=possibly Jennifer, possibly another alternate.

^b●=Answered beep, ()=unanswered beep, ○=additional rating completed.

motivational variables, which differ between people (10). This research has also shown that the 10-point wish-to-be-doing-something-else scale is a robust measure of the extrinsic/intrinsic dimension of motivation, with high scores indicating a lack of intrinsically motivating rewards for what one is doing (16). When we examined the correlations between the wish-to-be-doing-something-else scale and several mood adjectives for the alternates, we found that Taylor was again the most different from Jennifer Sue and Jennifer. Although the individual correlations were not necessarily significant, owing to small degrees of freedom, the differences among alternates were clearly apparent from the pattern of positive as opposed to negative values. That is, when Taylor wished to do what she was doing, she felt sad versus happy ($r=.58$), relaxed versus tense ($r=-.58$), and sociable versus lonely ($r=-.50$). In contrast, when Jennifer so wished, she felt happy ($r=-1.0$), tense ($r=.87$), and lonely ($r=.97$). In comparison, Jennifer Sue felt sad ($r=.58$), relaxed ($r=-.11$), and sociable ($r=-.17$). These differences between alters are as different as those re-

ported to occur between different persons previously studied with experiential sampling (10).

We compared the raters' global descriptions of the alternates to the self-report data. Some of the raters' descriptions were discrepant with each other and with the self-report data. For example, the therapist described Jennifer Sue as anxious, angry, depressed to the point of meeting *DSM-III* criteria for major affective disorder, and extremely troubled by chronic amnesia, headaches, fugues, and dissociative experiences. On the other hand, the second observer saw Jennifer Sue as relatively competent, energetic, and unimpaired. On the experiential sampling mood scales, however, Jennifer Sue's scores were not significantly different from those of the other alternates. She actually scored between Jennifer and Taylor on those self-ratings which always showed differences between the alters.

The greatest discrepancy between raters' predictions and the experiential sampling data occurred between Jennifer and Taylor. Clinically, Taylor seemed the most energetic, resourceful, assertive, humorous, and optimistic. She was a self-described "protector" who

usually gave the appearance of hypomania, cracking jokes and pacing through the room. Yet on self-reports, Taylor reported feeling the weakest, least alert, and least able to concentrate. Jennifer, who described herself as decorous and "rational" and who appeared clinically to be relatively emotionless, emerged on the experiential sampling data as the most alert, strongest, and most able to concentrate. In fact, the rank order of mood ratings for these two alters was the reverse of that predicted. When the alternates' main mood when signaled was assigned to global positive or negative categories and analyzed, Jennifer showed positive moods 66% of the time, compared to 20% of the time for both Jennifer Sue and Taylor.

DISCUSSION

The experiential sampling data suggest that switching of multiple personality alternates can be documented in a naturalistic study outside the usual clinical contexts. Although we encountered 21 alters in therapy, only seven ever answered the experiential sampling signal and only three were frequent responders. Indeed, the data operationalize Braun's definition of "host" personality (Jennifer Sue) as the one who has "executive control of the body the largest percentage of the time at a given time" (cited in reference 8). We also documented the phenomenon of coconsciousness (several alternates out together) that has been described in the clinical literature on multiple personality disorder (3, 8).

Our data complement the clinical observation that relatively few multiple personality alters have frequent or habitual access to full control of the body at times of reasonably good day-to-day functioning, although others may manifest themselves intrapsychically or coconsciously or only come out for particular activities, in response to specific situational triggers, or at times of stress (15). Stress may lead to more frequent switching in patients with multiple personality disorder. This in turn may lead to a vicious cycle in which the switching itself becomes an additional stressor, leading to more symptoms and dysfunctional behavior. Misdiagnosis may be quite likely at these times, as occurred with Ms. A (4, 15).

The multiple personality alters displayed some characteristics that were as different as those which occur between separate individuals who have been studied over time with experiential sampling (10). These ranged from style of marking forms and using rating scales to quantitative differences on the mood and motivational scales. Csikszentmihalyi, the leader of the group that developed experiential sampling, stated that he had never observed such varied responses within a single subject, despite his experience with the experiential sampling records of hundreds of subjects (personal communication).

The most puzzling aspect of the study was the discrepancy between the predicted mood states for

Jennifer, Jennifer Sue, and Taylor and the actual results. This may have been a transient circumstance related to Jennifer's and Taylor's insistence at that time in therapy that they had decided to fuse and exchange characteristics. If so, it is remarkable that experiential sampling captured the change. Another explanation is that the actual internal experience of multiple personality disorder alternates may be far more complex than the seemingly rational, internally consistent, and plausible manifest explanations for their behavior—especially as presented quite early in treatment (R.P. Kluff, personal communication).

These discrepancies may be related to the defensive function of the alter personality system—both in the everyday and intrapsychic senses of the term. Current research strongly indicates that multiple personality disorder develops as a childhood defense against overwhelming trauma—usually ongoing, severe child abuse (4, 8, 9). The giddy, apparently hypomanic protector alter may not only have functioned to handle vulnerability to new external dangers, as she proclaimed, but may also have represented an intrapsychic attempt to protect against a chronic internal experience of despair and helplessness. Except for conversion disorders—with which they are historically linked—the dissociative disorders may be the only *DSM-III* conditions in which phenomenology can be directly correlated with readily inferred intrapsychic events. Ironically, we generate the data for this hypothesis with experiential sampling, a behavioral method.

Because of the intrapsychic functions of the alter personality system, multiple personality disorder should not be conceptualized as a static entity. The alter personality system may be consistent and repetitive in many respects but fluid and dynamic in others. The relation between enduring and abiding characteristics of multiple personality disorder alternates and those activated by dynamic and situational factors is an important area for future research. This view may also help to reframe the longstanding debate over iatrogenesis in multiple personality disorder by leading to a clearer articulation of the specific dynamic, defensive, and representational aspects of the multiple personality disorder alters as they appear during psychotherapy.

The discrepancies between predicted mood states and actual self-reports illustrate concretely how easily these patients may mistakenly be given other *DSM-III* diagnoses instead of or in addition to multiple personality disorder. We had continued to consider the presence of true affective illness in this patient owing to the apparent depressive symptoms in Jennifer Sue and hypomanic symptoms in Taylor. The experiential sampling data suggest, however, that dissociative and dynamic factors led to apparent phenocopies of other psychiatric syndromes, as has been suggested in larger series of patients with multiple personality disorder (4, 8, 17). The implications are that clinicians should be cautious and that extensive, longitudinal, and in-depth clinical material should be gathered before symptoms

of multiple personality disorder are ascribed to or "explained" by the presence of other *DSM-III* diagnoses such as borderline personality disorder or primary affective disorder, as has been the case in several single case reports (18–20). With respect to axis II diagnoses, reports of larger series of patients with multiple personality disorder suggest that many axis II personality configurations, not just borderline personality disorder, may accompany multiple personality disorder (7).

Finally, this study illustrates the potential utility of experiential sampling for examining aspects of the treatment of multiple personality disorder and possibly of other conditions. The literature describes patients with mixtures of well-developed adaptational characteristics along with significant regressive potential who can become highly symptomatic in a relatively unstructured inpatient hospitalization. Regression may be countered by setting clear treatment goals and firm limits, which may include an enforced discharge date from the hospital (21, 22). During her NIMH inpatient stay, Ms. A became difficult to manage as dysfunctional, highly symptomatic alters became very prominent. It was finally decided to give the patient a firm 30-day limit for her remaining hospitalization, with either discharge or transfer to another facility mandated at the end of that time. The experiential sampling study occurred during the final hospital month. Although an experiential sampling baseline was not obtained before the study, in this instance the experiential sampling data fit well with the clinical data. During the last month in the hospital, the symptomatic and dysfunctional alters primarily retreated into the background. Behavior across the whole alternate personality system of the patient was relatively adaptive and symptom free.

In summary, we have shown that experiential sampling is a useful, relatively simple method for studying aspects of the phenomenology of multiple personality disorder that can easily interface with other research methods such as psychophysiological measures and single-time-of-day rating instruments. In addition, experiential sampling may show promise in the study of the phenomenology and treatment of other psychiatric disorders, especially those with frequent state changes or symptoms apparently generated by behavioral triggers.

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Diazepam-Induced Amnesia: A Neuropharmacological Model of an "Organic Amnestic Syndrome"

Owen M. Wolkowitz, M.D., Herbert Weingartner, Ph.D., Karen Thompson, B.S.,
David Pickar, M.D., Steven M. Paul, M.D., and Daniel W. Hommer, M.D.

Diazepam has well-known amnestic properties. These effects, however, are selective for certain psychobiologically distinct memory functions. In this study, incremental doses of diazepam administered to 10 normal volunteers selectively impaired anterograde episodic memory and attention while totally sparing access to information in long-term memory (semantic or knowledge memory). This pattern of disruption mimics that seen in patients with organic amnesias and is in sharp contrast to the pattern seen in patients with dementia. These findings provide a framework for defining specific psychobiological determinants of cognitive failure.
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The ability of the benzodiazepines to impair memory has been amply demonstrated (1-3). Studies to date have largely been parametric rather than mechanism oriented, with some exceptions (4, 5). Our growing awareness of the different components of memory, which may be psychobiologically distinct, and the development of measures to assess these components independently now allow us more systematically to characterize the benzodiazepine-induced cognitive effects. This is important both for the development of a better understanding of the specific brain and behavioral changes produced by benzodiazepines and for what it can teach us about the psychobiology of memory. Such research may also be useful in furthering our understanding of the pathologies of memory by providing models for naturally occurring amnestic disorders.

The distinction between "episodic" and "knowl-

edge" memory is heuristically important. Episodic memory, the focus of most studies of memory, represents the memory of specific events. It includes information about when the events occurred, preceding and subsequent events, and the context of the events (6). The representation of knowledge in long-term memory, or knowledge memory, appears to be rather different from episodic memory and appears to be a psychobiologically distinct system. Information in knowledge memory includes facts, language, and perhaps procedures and rules. This memory system represents the organized, schematized previous experiences that make it possible to interpret and encode ongoing events (7). These two memory stores may be differentially affected by certain drugs or disease processes. Organic amnestic syndromes (e.g., Korsakoff's syndrome and postencephalitic amnesia) are characterized by marked deficits in episodic memory with relative sparing of knowledge memory (8), whereas progressive dementias are characterized by marked deficits in both (9). Other illnesses, such as Parkinson's disease or depression, may affect still other components of memory such as "effortful" (i.e., requiring sustained participation by the subject) as opposed to "incidental" learning (10, 11).

The memory deficits induced by diazepam or similar benzodiazepines such as lorazepam may mimic those seen in the organic amnestic syndrome (4, 12). The present study and methods were designed with the above distinctions in mind, i.e., to contrast the effects of diazepam on the component processes of memory.

Another purpose of the present study was to differentiate the cognitive versus the noncognitive impairments contributing to the decline in memory task performance seen with diazepam. Levels of sedation or arousal can influence memory task performance; some studies (13, 14) have suggested an association between sedation and subsequent amnesia with diazepam, while others have suggested that memory may be impaired even in the absence of marked sedation (2, 3) or at least to a degree not accounted for by the observed inattentiveness (12). The dose-response paradigm in the present study was selected to assess the relative sensitivities of the different cognitive and noncognitive components of memory to diazepam. This strategy assesses whether the attentional-arousal defi-

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cits and the mnemonic deficits occur at the same or different threshold doses and therefore suggests the presence or absence of an obligatory relationship between them.

METHOD

Subjects were 10 normal volunteers (three men, seven women; age range=22–35 years) who gave informed consent to participate after a discussion of the study and the probable effects of intravenous diazepam. The subjects had no medical illnesses or history of psychiatric illness, alcoholism, or drug abuse. They had taken no benzodiazepines for 6 months before the study or other medications for 2 weeks before the study. They were instructed to abstain from beverages containing caffeine or alcohol for 36 hours before each study day. All subjects were studied in the morning after an overnight fast.

Subjects were tested on 2 days, separated by at least 1 week. On 1 test day they received diazepam and on the other test day they received normal saline in a single-blind manner. The order of administration of active drug versus placebo was randomized.

Subjects initially practiced all memory tests until they attained a stable performance plateau. On each test day, a baseline memory test was administered 60 minutes after placement of an intravenous catheter that was kept patent with heparin. The schedule of subsequent injections and memory tests is listed in appendix 1.

Memory tests were performed after cumulative intravenous diazepam doses of 8.8 µg/kg, 35.1 µg/kg, and 140.1 µg/kg (0.625, 2.5, and 10.0 mg in a 70-kg individual). In addition to memory testing, other measures of benzodiazepine effect, such as eye saccadic movement velocity, plasma cortisol and growth hormone concentrations, and self-rated sedation (measured with a 100-mm visual analogue scale) were assessed after each successive diazepam injection. These have been discussed in a separate report (15).

At each test point, subjects were read a list of 18 words, all from the same category, at a rate of one word every 3 seconds. Six of these 18 words were read twice, and six were read only once. For each memory test, a list was selected from a different category to minimize interlist interference. During the reading of the list, subjects nonverbally indicated to the tester whenever they heard a word repeated. This is a test of attention or vigilance. Following that, subjects were asked to generate a list of their own in response to a different category heading that was supplied to them. This task lasted 1½ minutes and has been shown to be a sensitive measure of knowledge memory (9). Following that task, which also served to distract the subjects from mentally rehearsing the original list, subjects were asked to freely recall as many words as possible from the original list. This is a test of effortful episodic memory. Finally, in a recognition task, subjects were

asked to discern between previously presented words and an equal number of words from the same category that had not been presented previously. For words identified as previously presented, subjects were asked to remember if they were originally presented once or twice. This latter task assesses automatic or incidental memory. The memory test, then, allows a comparative assessment of diazepam's effect on several distinct components of information processing: attention-vigilance, effortful versus automatic processing, free versus facilitated (i.e., recognition) recall, and episodic versus semantic memory.

Data were analyzed by analysis of variance (ANOVA) with repeated measures by a computer with a standard statistical program (Statistical Analysis System).

RESULTS

Performance on all measures was similar at all four time points on the placebo day and on the baseline test session of the diazepam day (n.s.). Therefore, for purposes of analysis, these five time points were combined into one "baseline measure" for comparison with each of the postdiazepam time points. No carryover effect of diazepam was noted for those subjects who were tested with diazepam on the first test day and placebo on the second. Diazepam significantly decreased performance on attention ($F=6.15$, $df=3$, 27 , $p<.003$), recognition ($F=5.71$, $df=3$, 27 , $p<.004$), and frequency monitoring (automatic processing) ($F=3.50$, $df=3$, 27 , $p<.03$). The rate of intrusions into free recall was significantly increased by diazepam ($F=4.63$, $df=3$, 27 , $p<.01$). The number of words correctly recalled freely was nonsignificantly decreased by diazepam; however, when the number of words was corrected for the number of intrusions, the resulting measure, which more accurately reflects recall as opposed to "correct" guessing, was significantly decreased by diazepam ($F=3.76$, $df=3$, 27 , $p<.03$) (table 1). Subjects were reliably able to estimate the accuracy of their performance. Confidence ratings of free recall declined in relation to dose of diazepam ($F=5.34$, $df=3$, 27 , $p=.005$). In marked distinction to diazepam's significant deleterious effect on measures of episodic memory, knowledge memory was spared ($F=1.57$, $df=3$, 27 , n.s.) (table 1). In fact, at the lowest dose of diazepam, according to post-hoc Scheffé tests there was a suggestion of a mild enhancement of knowledge memory (baseline versus dose 2, $p<.08$; dose 2 versus dose 3, $p<.05$). Post-hoc Scheffé tests also revealed significant effects of diazepam on attention, intrusions, recognition, automatic processing, and free recall (corrected for intrusions) at the highest dose of diazepam only (table 1). These results are diagrammed in figure 1, in which standardized units of change from baseline performance (T scores) are used to graphically highlight the differentiated nature of diazepam's effect on distinct components of memory.

TABLE 1. Effects of Diazepam on Attention and Episodic and Knowledge Memory in 10 Normal Subjects

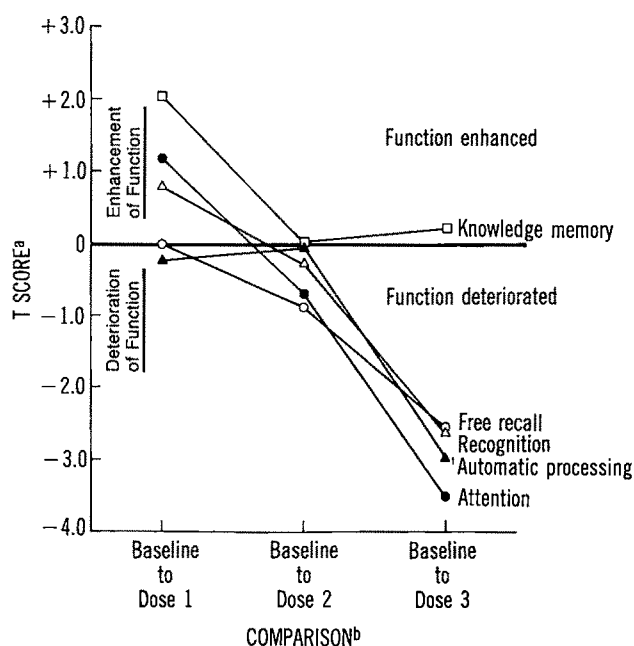
Time	Number of Words ^a									
	Episodic Memory									
	Attention		Free Recall		Recognition		Automatic Processing		Knowledge Memory	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Baseline	5.10	0.57	7.04	1.49	11.20	0.63	0.38	0.16	14.58	2.34
Dose 1 (8.8 µg/kg)	5.50	0.98	6.70	2.78	11.40	0.98	0.36	0.22	18.90	6.76
Dose 2 (35.1 µg/kg)	4.90	0.88	5.80	2.53	11.10	1.58	0.38	0.25	14.80	6.32
Dose 3 (140.1 µg/kg)	4.00 ^b	1.17	4.30 ^c	3.44	10.10 ^b	1.58	0.05 ^c	0.32	15.20	7.08

^aValues for free recall corrected for intrusions. Values for automatic processing are differences between the mean reported frequency of twice-presented words and that of once-presented words.

^b $p < .01$ (post-hoc Scheffé tests).

^c $p < .05$ (post-hoc Scheffé tests).

FIGURE 1. Effect of Diazepam on Attention and Episodic and Knowledge Memory in 10 Normal Subjects



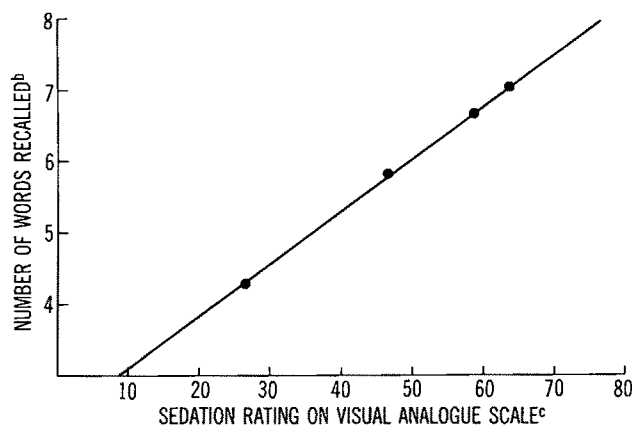
^aSignifies standardized units of change from baseline performance (at baseline all functions would have a T score equal to zero).

^bDose 1=8.8 µg/kg; dose 2=35.1 µg/kg; dose 3=140.1 µg/kg.

As can be seen, there was no differential threshold dose for diazepam's effects on attentional versus mnemonic performance, effortful versus incidental learning, or free versus facilitated recall. Finally, self-ratings of sedation were significantly inversely related to memory performance ($r = .99$, $df = 2$, $p < .01$) (figure 2).

DISCUSSION

We observed a highly differentiated unfolding of cognitive impairment in response to increasing doses of diazepam. Diazepam produced a marked deficit in episodic memory, yet despite this dense amnesia (some subjects did not even recall having heard a given

FIGURE 2. Correlation Between Self-Rated Sedation and Recent Memory Following Diazepam Administration^a

^a $r = .99$, $df = 2$, $p < .01$.

^bCorrected for intrusion errors.

^cLower rating indicates more sleepiness; higher rating indicates more alertness.

memory list), knowledge memory was totally unimpaired. This reinforces the emerging notion that these two stores are psychobiologically distinct (i.e., dependent on different chemical or anatomical substrata). It is of clinical interest that our volunteers were accurately able to assess the degree of their cognitive impairment while under the influence of diazepam.

Our data also support the distinction between acquisition or consolidation of new information, which is deleteriously affected by diazepam, and retention and retrieval of previously acquired information, which is spared (16). Diazepam did not differentially affect effortful versus incidental processing. Disorders such as depression and Parkinson's disease preferentially impair performance on effort-demanding tasks, perhaps as a function of diminished catecholaminergic activity (17). Our study suggests that the amnesic syndrome produced by diazepam is psychobiologically different, i.e., is operating through a different (or an additional) mechanism.

In this study, we observed a significant impairment

in attention at the same dose of diazepam that produced impairments in episodic memory. Because no disjunction of effects at different threshold doses was observed, we cannot rule out the possibility that the attentional deficit underlies the deficit in memory performance. Indeed, the significant relationship between self-rated sedation and memory impairment seems to support this notion and would be in agreement with other reports noting such a relationship (13, 14). Previous research into this issue has been inconclusive; several reports (2, 3, 12, 18) also suggested at least partial independence of these effects. Studies using sleep deprivation (19, 20) have shown that sleepiness alone does not impair recent memory, and preliminary findings in our laboratory suggested that caffeine may attenuate the attention impairment produced by diazepam without altering the effect on episodic memory. Benzodiazepine receptors are located in the reticular formation as well as in the hippocampus (21). The reticular formation is responsible for maintaining a state of CNS arousal. It is therefore not surprising to find that diazepam affects both memory and arousal.

It is uncertain if the observed memory impairment is unique to benzodiazepines. Other CNS depressants such as barbiturates, alcohol, and ether also impair anterograde amnesia, although perhaps to a lesser degree than do benzodiazepines (22–27). However, several lines of evidence suggest that the memory deficit seen following benzodiazepine administration is secondary to specific effects at the benzodiazepine receptor. It is now generally accepted that benzodiazepines bind to specific receptors in the CNS (28). These receptors are present in a high density in the hippocampus (21), and Clark et al. (29) suggested that benzodiazepine-induced changes in hippocampal neural firing may account for their effects on memory. We have presented data elsewhere (15) showing highly significant correlations between the dose-dependent effects of benzodiazepines on memory and benzodiazepine-receptor-mediated effects on eye saccadic movement velocity and plasma growth hormone and cortisol. These data, as well as the finding of a marked attenuation of benzodiazepine-induced amnesia by the specific benzodiazepine receptor antagonist RO15-1788 (30), strongly suggest involvement of the benzodiazepine receptor in the memory effects of diazepam.

The observed pattern of memory disruption, i.e., impairment of episodic memory with sparing of knowledge memory, is similar to that seen in organic amnesias such as Korsakoff's disease or postencephalitic amnesia and may provide a pharmacologic model of these disorders. This is consistent with reports by Lister and File (4) and Brown et al. (12). Piercy (31), in discussing the mnemonic abilities preserved in organic amnesias, noted that although these patients were "extremely inefficient at describing on request unique events in their lives which occurred more than two or three minutes ago" (p. 5), they were "able to utilize information which has been held in storage over a

considerable period of time" (p. 7). Theoretically, this phenomenologic similarity might be secondary to disturbances of hippocampal activity both in organic amnesias (32, 33) and in diazepam-induced amnesia (29).

An emerging theme in the psychopharmacology of cognition is that different drugs may affect memory in distinctive patterns and may model different disorders (34). For example, scopolamine, an anticholinergic drug, impairs semantic as well as episodic memory in normal humans (35), modeling the pattern of cognitive deficits seen in senile dementia of the Alzheimer type. These two drugs, diazepam and scopolamine, may provide pharmacologic models of two very different clinical syndromes (36). Observation of the patterns of impairment produced by drugs, coupled with a knowledge of the mechanism of action and receptor distribution of the drug, may provide the keys to unraveling the mechanisms of memory.

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APPENDIX 1. Experimental Protocol for Testing Diazepam-Induced Amnesia

- 9:15 a.m.: intravenous line inserted.
- 10:15 a.m.: baseline memory test.
- 10:30 a.m.: infusion 1 (saline or 4.4 µg/kg of diazepam).
- 10:45 a.m.: infusion 2 (saline or 4.4 µg/kg of diazepam).
- 10:53 a.m.: memory test 2.
- 11:00 a.m.: infusion 3 (saline or 8.8 µg/kg of diazepam).
- 11:15 a.m.: infusion 4 (saline or 17.5 µg/kg of diazepam).
- 11:23 a.m.: memory test 3.
- 11:30 a.m.: infusion 5 (saline or 35 µg/kg of diazepam).
- 11:45 a.m.: infusion 6 (saline or 70 µg/kg of diazepam).
- 11:53 a.m.: memory test 4.

The Dexamethasone Suppression Test as a Monitor of Clinical Recovery

Eric D. Peselow, M.D., Ngaere Baxter, Ph.D., Ronald R. Fieve, M.D.,
and Faouzia Barouche, M.D.

To evaluate the dexamethasone suppression test (DST) as an aid in monitoring clinical recovery, the authors evaluated 127 outpatients with major depression who received the DST during depression and after clinical recovery. Although DST response varied among the 73 patients who met the Research Diagnostic Criteria for definite endogenous depression, their mean postdexamethasone plasma cortisol level was significantly higher during depression than after recovery. However, the DST's utility in monitoring long-term outcome was not great, as there was a high chance of remaining stable for 6 months after recovery regardless of cortisol value during depression or after recovery.

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Over the past 10 years, the dexamethasone suppression test (DST) has been widely employed as a clinical and research tool in evaluating overactivity of the hypothalamic-pituitary-adrenal axis in patients with major affective disorder. Despite varying methods used to categorize depression, inadequate suppression of cortisol the day after dexamethasone administration has been demonstrated in 25%–60% of patients with major affective disorders (1).

Other important findings involving the DST suggest that this neuroendocrine disturbance resolves with clinical improvement of the depression. If this is true, the DST might give the clinician a more objective measure of evaluating depression and recovery than clinical observation alone.

Received June 14, 1985; revised Dec. 5, 1985, and May 27, 1986; accepted June 27, 1986. From the Department of Psychiatry, New York University School of Medicine; and the New York State Psychiatric Institute, New York. Address reprint requests to Dr. Peselow, 1322 East 84th St., Brooklyn, NY 11236.

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Several studies reporting on the relationship of DST status to clinical recovery either have been open (2) or have been retrospective and have used raters blind to DST results (3, 4), and they have usually selected patients who initially had positive DSTs. The purpose of the evaluation reported here was to examine in a double-blind prospective manner the cortisol responses of depressed outpatients after dexamethasone administration during an acute depressive episode and after clinical recovery. The patients involved in this study were followed for up to 6 months after recovery from their index depressive episodes.

METHOD

Over 4 years we prospectively studied cortisol responses to dexamethasone during acute depression and after clinical recovery in 127 outpatients. All patients gave voluntary informed consent to treatment and DST administration. All patients studied were diagnosed as having major depressive disorder by three trained raters and met the Research Diagnostic Criteria (RDC) (5) for major depressive disorder. In addition, all patients had a score of 16 or higher on the Hamilton Rating Scale for Depression (6) and required antidepressant treatment. Overall, 74 patients met the RDC for recurrent unipolar depression, 28 met the RDC for bipolar I illness, and 25 met the RDC for bipolar II illness.

At the onset of the index depressive episode, the patients were rated with the Hamilton depression scale, Beck self-rating scale (7), and a 4-point global severity scale for depression rated by both the treating doctor and the patient (for severe, moderate, and mild depression and euthymic mood—points 1–4, respectively). In addition, the patients were evaluated with an endogenous symptom scale abstracted from the Schedule for Affective Disorders and Schizophrenia (SADS) (8).

After completion of these ratings, the patients were given 1 mg of dexamethasone at 11:00 p.m. and returned the following day at 4:00 p.m. to provide blood for an assay of plasma cortisol as recommended for outpatients by Carroll et al. (9, 10). To ensure accuracy and compliance, the patients were questioned

TABLE 1. Age and Depression Ratings of 127 Patients With Endogenous (N=73) or Nonendogenous (N=54) Depression

Variable	Total Group		Endogenous		Nonendogenous		Analysis	
	Mean	SD	Mean	SD	Mean	SD	t (df=125)	p
Age (years)	38.03	12.4	39.47	13.8	36.07	8.8	1.58	>.1
Hamilton score	23.66	7.8	26.18	8.6	20.26	5.1	4.51	<.001
Beck score	25.00	10.0	27.78	10.3	21.24	4.4	3.96	<.001
Endogenous score	34.29	6.7	38.97	4.3	27.96	4.4	14.24	<.0001
Global depression rating ^a								
Physician	2.07	1.1	1.75	0.8	2.50	0.7	6.38	<.0005
Patient	1.91	1.0	1.69	0.8	2.21	0.7	3.86	<.001

^aLower score indicates more severe depression.

by two observers as to whether and when they took the dexamethasone.

Although attempts were made to keep all patients medication-free for as long as clinically possible before testing during the depressed phase, this was clinically impractical because many patients had histories of severe depression and mania. Overall, 97 of the 127 patients had been medication-free for at least 5 days before the DST. The remaining patients were taking lithium, antidepressants, or lithium plus antidepressants—medications that have been shown to not interfere with the DST (10).

The patients were then treated clinically with amitriptyline, imipramine, or desipramine with or without lithium carbonate on an open basis. Those who recovered and remained free of depressive symptoms after 3–6 weeks of treatment were given the same ratings and another DST after 2 weeks of sustained clinical recovery. Overall, the DST was repeated after 36–56 days of active treatment (mean, 44 days). Clinical recovery was defined as a Hamilton depression rating of 10 or less and a 50% or greater improvement on the Hamilton and Beck scales.

The 127 patients who recovered from their depressive episodes were part of a sample of 240 patients with major depressive episodes who received DSTs over 4 years (11). The 113 patients not included in the present analysis either did not recover with standard antidepressant therapy over 3–6 weeks (N=55), dropped out (N=43), or recovered but for varied reasons did not have a repeat DST (N=15).

We then followed the 127 patients who recovered from the depressive episodes for up to 6 months after clinical recovery; during this time they received the same doses of medication to which they had responded. Both lithium and tricyclic levels were determined every 4–6 weeks during this follow-up to ensure compliance. Over the 4 years of this study all raters and patients remained blind to DST results for at least 6 months after clinical recovery.

For the purposes of this evaluation, an abnormal DST was defined as a 4:00 p.m. plasma cortisol level of 5 µg/dl or higher. This criterion gave the best proportion of sensitivity and specificity (35.6%/87.0%); at 4 and 6 µg/dl these proportions were 37.0%/81.5% and 30.1%/88.9%, respectively. Plasma cortisol was measured by means of the competitive protein binding

method of Murphy (12). The between-assay coefficient of variation was 8%.

Statistical analyses for plasma cortisol levels were done on both raw and log-transformed values. Since the log-transformed cortisol values better fitted a normal distribution, these were used for further analysis.

RESULTS

To isolate a specific subgroup with a greater frequency of abnormal DSTs (1, 9, 10), we divided the group into the 73 patients who met the criteria for definite RDC endogenous depression and the 54 patients who were considered nonendogenous. There were 45 men and 28 women in the endogenous subgroup and 28 men and 26 women in the nonendogenous subgroup; their ages and depression ratings are shown in table 1. The endogenous subgroup was more severely depressed, as evidenced by statistically significantly worse scores on the Hamilton, Beck, endogenous, and global severity ratings than those of the nonendogenous group. The mean DST cortisol value during depression was similar in the unipolar, bipolar II, and bipolar I patients. The proportions of positive DSTs did not significantly differ among these three diagnostic groups (24.3%, 24.0%, and 32.1%, respectively; $\chi^2=0.65$, $df=2$, $p=.5$) or between the patients who were included in the present study (those who recovered from depression) and those who either did not recover or dropped out (26.0% and 24.8%; $\chi^2=0.002$, $df=1$, $p=.9$).

Table 2 notes the patients' medication status during the depressive episode. The patients who had been drug-free for more than 2 weeks, those who had been drug-free for 5–14 days, and those who were still receiving psychotropic agents did not differ statistically in rates of positive DSTs. Thus, undergoing withdrawal from a psychotropic drug did not lead to a higher frequency of abnormal DSTs in the 5–14-day group. In addition, treatment with a tricyclic alone and treatment with lithium plus tricyclic at the time of the DST yielded similar rates of positive DSTs. Table 3 shows the rate of DST nonsuppression after clinical recovery for each drug treatment given.

Table 4 indicates that there was no consistent response to the DST during depression and after clinical

TABLE 2. Relationship Between Medication Status and DST Result for 127 Depressed Patients

Medication Status at Time of DST	N	Positive DST		Negative DST	
		N	%	N	%
Drug free more than 2 weeks	60	15	25.0	45	75.0
Drug free 5 days to 2 weeks	37	11	29.7	26	70.3
Taken off lithium alone	13	4	30.8	9	69.2
Taken off tricyclic alone	14	5	35.7	9	64.3
Taken off lithium and tricyclic	10	2	20.0	8	80.0
Taking medication	30	7	23.3	23	76.7
Lithium alone	14	3	21.4	11	78.6
Tricyclic alone	9	2	22.2	7	77.8
Lithium and tricyclic	7	2	28.6	5	71.4

TABLE 3. Relationship Between Type of Drug Treatment and DST Result During Depression and After Clinical Recovery for 127 Patients

Treatment	N	Positive DST			
		During Depression		After Recovery	
		N	%	N	%
Tricyclic alone	74	18	24.3	10	13.5
Desipramine	15	4	26.7	3	20.0
Imipramine	37	9	24.3	5	13.5
Amitriptyline	22	5	22.7	2	9.1
Tricyclic plus lithium	53	15	28.3	8	15.1
Imipramine plus lithium	18	5	27.8	3	16.7
Amitriptyline plus lithium	20	6	30.0	3	15.0
Desipramine plus lithium	15	4	26.7	2	13.3

recovery for the total sample of 127 patients or for the endogenous subgroup. Of the 73 endogenous patients, 20 (27.4%) had abnormal DSTs during depression and normal DSTs after clinical recovery, six (8.2%) had abnormal DSTs both times, 43 (58.9%) had normal DSTs both times, and four (5.5%) had normal DSTs during depression and abnormal DSTs after clinical recovery. Of the 54 nonendogenous patients, 42 (77.8%) had normal DSTs both during depression and after clinical recovery.

The mean \pm SD 4:00 p.m. postdexamethasone raw plasma cortisol levels during depression in the endogenous and nonendogenous patients were 4.85 ± 3.4 and 2.94 ± 2.2 μ g/dl, respectively. The difference between the log-transformed values was statistically significant ($t=3.44$, $df=125$, $p<.001$, Student's t test for uncorrelated data), in accordance with previous findings (9, 10). For the nonendogenous group, the cortisol levels during depression and after clinical recovery were essentially equivalent (2.94 ± 2.2 versus 3.04 ± 2.2 μ g/dl; comparison of log-transformed values: $t=0.25$, $df=53$, $p>.75$, paired t test for related samples). For the endogenous group, there was a statistically higher 4:00 p.m. cortisol level during depression than after clinical recovery (4.85 ± 3.4 versus 2.85 ± 2.6 μ g/dl; comparison of log-transformed values: $t=4.32$, $df=72$, $p<.0001$, paired t test for related samples). However, this pattern, although statistically significant, did

not apply to many of the patients; 25 of the 73 patients in the endogenous subgroup had higher 4:00 p.m. cortisol levels after clinical recovery than during depression (four original suppressors converted to non-suppression upon clinical recovery).

Table 4 also shows the 6-month follow-up for the 127 patients. Of the original 127 patients, 34 (26.8%) dropped out while euthymic before the 6-month follow-up was completed. Of the 34 dropouts, 22 did not return for treatment and 12 either lowered their medication dose because of side effects or refused medication. Of the remaining 93, 66 remained stable for 6 months and 27 (29.0%) relapsed. The mean \pm SD numbers of depressive episodes in the 2 years before the current depressive episode of the patients who relapsed and the nonrelapsers were similar (1.22 ± 0.98 versus 1.06 ± 0.95 ; $t=0.73$, $df=91$, $p>.40$, Student's t test). In addition, the average length of time depressed in the prior 2 years was not significantly different for the 27 relapsers and the 66 nonrelapsers (3.52 ± 3.9 versus 2.72 ± 3.4 months; $t=1.00$, $df=91$, $p>.25$).

There was no significant difference in relapse rate over the 6-month period among the four groups ($\chi^2=1.26$, $df=3$, $p>.7$). However, as can be seen from table 4, the patients who had positive DSTs after apparent clinical recovery (groups 2 and 4) had a 10.2% higher rate of relapse (six of 16, 37.5%) than those who had negative DSTs (groups 1 and 3) upon apparent clinical recovery (21 of 77, 27.3%). This difference was not statistically significant ($\chi^2=0.26$, $df=1$, $p>.5$).

DISCUSSION

Cumulative data (13, 14) suggest that patients who have diagnoses of endogenous or melancholic depression have a higher frequency of abnormal DSTs than patients with other psychiatric classifications. We used this rationale for dividing our group of heterogeneous depressed outpatients into those who met the RDC for definite endogenous depression during depressive episodes and those who did not.

Only a few studies have examined the DST during depression and after treatment. Albala et al. (4) studied six patients with initial positive DSTs who were treated with ECT. The DST responses of the five patients who responded to ECT all normalized, whereas the one who did not respond continued to have a positive DST. Greden et al. (15) examined 21 patients with initial positive DSTs. Of the 17 whose DSTs normalized after antidepressant treatment, 15 had good responses, as did only two of the four whose DSTs did not normalize. Klein et al. (16) studied 81 patients who received DSTs during depression and after varied clinical treatments and found a strong correlation between improvement and decreasing post-dexamethasone plasma cortisol level. Our findings generally agree with those from the studies just described, as we found that for the patients with endogenous depression the mean plasma cortisol value after

TABLE 4. DST Pattern and Follow-Up Course for 127 Depressed Patients Who Recovered

Group	DST Status		Depressive Subtype			Course			
	During Depression	After Recovery	Endogenous	Nonendogenous	Total	Dropped Out	Followed 6 Months		
							N	Relapsed N	%
Group 1	Positive	Negative	20	4	24	4	20	6	30.0
Group 2	Positive	Positive	6	3	9	0	9	4	44.4
Group 3	Negative	Negative	43	42	85	28	57	15	26.3
Group 4	Negative	Positive	4	5	9	2	7	2	28.6
Total			73	54	127	34	93	27	29.0

dexamethasone administration was significantly higher during depression than after clinical recovery.

The further question of whether the DST value predicts long-term success is an intriguing one. Most studies to date suggest that if a positive DST does not normalize, even in the face of apparent clinical improvement, a more ominous course is suggested. Goldberg (2) studied eight patients with initial positive DSTs who responded to antidepressant treatment. Upon clinical recovery, the DST was repeated, and of the eight patients, five had normal DSTs but three did not. When Goldberg discontinued the antidepressant treatment for 2 months, the five normal DST patients all remained stable, while the three with persistent positive DSTs all relapsed. Greden et al. (3) studied 14 patients with initial positive DSTs who were treated with various antidepressants or ECT. Upon apparent clinical recovery, the DSTs for 10 of the 14 patients had normalized. Eight of the 10 patients whose DSTs had normalized remained stable (one of the other two had stopped taking medication), and all four with nonnormalized DSTs relapsed. Yerevanian et al. (17) studied 14 patients with initial positive DSTs who were treated with various antidepressants and/or ECT. Upon apparent clinical recovery, the DST was repeated; 10 of the 14 continued to have positive DSTs. While three of the four patients with normalized DSTs remained stable, all 10 with persistently positive DSTs relapsed. Holsboer et al. (18) studied 20 patients with initial positive DSTs. The 16 whose DSTs normalized upon apparent clinical recovery all remained stable, whereas the four whose DSTs remained positive all relapsed. In contrast, Coryell and Zimmerman (19), in following 16 patients who had initial positive DSTs during depression and were successfully treated with ECT, noted that only one of the nine whose DSTs normalized sustained clinical improvement, versus six of the seven whose DSTs did not normalize.

In our study DST status during depression and after clinical recovery did not predict 6-month relapse. No matter what DST group an individual fell into (positive/negative, positive/positive, negative/negative, or negative/positive during depression and after recovery, respectively), there was no greater or lesser chance of 6-month stability. If we consider only patients who started with positive DSTs, which may be the more important group (groups 1 and 2), six (30%) of the 20

whose DSTs normalized relapsed during the 6-month course, as did four (44%) of the nine whose DSTs did not normalize. Although there was a trend toward DST normalization predicting a better 6-month outcome, and although statistical significance might have been achieved if our sample were increased tenfold, the relapse rates were at variance with those in the reports we have cited. Baldessarini and Arana (13) pooled the data from 10 such studies and noted that a persistently positive DST predicted a poor outcome for 79% of the patients (26 of 33), while the risk of relapse was only 25% (11 of 44) if the DST converted to normal ($p=9 \times 10^{-6}$). Our figures were 44% (four of nine) and 30% (six of 20), respectively.

There are a few possible explanations for this difference. First of all, our sample consisted of depressed patients treated in an outpatient setting, whereas the patients in the other studies were initially all inpatients. Second, the other studies did not control for outpatient treatment and used various modalities, but we attempted to keep as many patients as possible on the medication to which they had responded over 6 months, controlling for compliance by measuring plasma levels of antidepressants and lithium. Since it is estimated that there is an 80% rate of sustained improvement with continuation therapy but only 40% with placebo over 6 months (20), it is possible that keeping a patient on the medication to which he or she had responded prevented relapse and clouded the DST results. The study by Goldberg (2), which discontinued antidepressant treatment upon clinical recovery, might be more meaningful if replicated because it suggested that normalization of the DST would allow the clinician to discontinue medication safely, whereas a persistently positive DST would indicate the need for continued somatic treatment. In contrast, while sustaining maintenance therapy in our study may have prevented relapse by itself, regardless of the DST, the fact that many of the other investigators (3, 17–19) frequently changed treatments during follow-up (not always giving the patient the medication or modality to which he or she had responded as maintenance treatment) could have been responsible for relapse, regardless of normalization of the DST or not.

The low sensitivity for the DST in depressed outpatients found here is not very much at variance with the existing literature. While Carroll et al. (9, 10) reported

a 49% sensitivity for depressed melancholic outpatients, other investigators noted rates equal to (21) or lower than (22, 23) the 35.6% (26 of 73) sensitivity for our endogenous subgroup. A possible reason for lower sensitivity may be that abnormal DSTs seem to correlate with more severe depressive illness (11, 16), and outpatients by definition generally have less severe symptoms than inpatients. However, the low sensitivity and diagnostic heterogeneity of outpatients by no means render the DST useless for this group. Since outpatients represent the majority of depressed patients given drug treatment, the presence of an objective measure to monitor clinical course would be useful to the treating psychiatrist. Indeed, it is felt that for the depressed outpatient various forms of psychotherapy—i.e., cognitive therapy (24) and interpersonal psychotherapy (25)—may be as efficacious as antidepressants. Thus, if the DST is useful in predicting which form of treatment—pharmacotherapy, psychotherapy, or cognitive therapy—should be used for short- and long-term treatment of depressed outpatients, clinical judgment could be aided by an objective measure so as to give the best possible outcome for the patient. A study by Shrivastava et al. (26) noted that none of nine patients with positive DSTs responded to placebo. Thus, a positive DST may suggest the need for active treatment. In a study by Rush (27) involving 14 patients, response to cognitive therapy occurred in none of the five patients with positive DSTs but in eight of the nine with negative DSTs. However, a recent study by Georgotas et al. (28) noted that a positive or negative DST did not predict response to nortriptyline, phenelzine, or placebo.

In summary, despite variance among individual patients with endogenous depression, they had a statistically higher mean postdexamethasone plasma cortisol level during depression than after clinical recovery. However, the utility of the DST as a monitor of long-term outcome was not great for our group, as there was a high chance of remaining stable for 6 months after a depressive episode regardless of DST value during depression and after improvement.

The relevance of a positive versus a negative DST in predicting long-term outcome requires further evaluation in the form of double-blind prospective trials.

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Clinical Predictors of Suicide in Patients With Major Affective Disorders: A Controlled Prospective Study

Jan Fawcett, M.D., William Scheftner, M.D., David Clark, Ph.D.,
Don Hedeker, Robert Gibbons, Ph.D., and William Coryell, M.D.

The authors report prospective uniform clinical data differentiating 25 patients who committed suicide from 929 patients who did not in a group of 954 patients with major affective disorder followed for an average of 4 years in the Collaborative Program on the Psychobiology of Depression. Eight (32%) of the suicides occurred within 6 months and 13 (52%) within 1 year of entry into the study. Hopelessness, loss of pleasure or interest, and mood cycling during the index episode differentiated the suicide group. Diagnostic subcategories, suicidal ideation at entry to the study, suicide attempts during current or past episodes, and medical severity of prior attempts did not differentiate the suicide group. (Am J Psychiatry 1987; 144:35-40)

Suicide is a major public health problem as well as a serious challenge for the clinical psychiatrist. The problem for the clinician is the accurate identification of individual patients at high risk for suicide so as to permit timely intervention. Retrospective studies of suicide have shown that it occurs in association with a diagnosable psychiatric disorder, usually depression, schizophrenia, or alcoholism (1-4). A review of follow-up studies (5) showed that the lifetime incidence of suicide among depressed patients is 15%. This

annual rate is 3.5-4.5 times higher than that of other psychiatric diagnostic groups and 22-36 times higher than the general population rate (6, 7). According to studies available for review in 1977, no subtype of depression has been found to be associated with greater risk for suicide, but there is suggestive evidence that adequate psychiatric treatment has been successful in lowering the risk of suicide (7-11).

Although suicide is relatively frequent in depressed patients, it still has a statistically low base rate and, therefore, may be statistically unpredictable on an individual basis with cross-sectional measures (12, 13). Nonetheless, the clinician's challenge is not only to discern which individuals are at greatest suicidal risk within a high-risk group but also to recognize the time of greatest risk. Moreover, this prediction must be made with enough certainty to initiate effective intervention despite the limitations of prediction techniques. The more complete and valid our clinical profile of the patient on the verge of suicide, and the more clinical predictors can be applied to specific time periods, the more successful the clinician may be in recognizing the "needle in the haystack" and taking timely preventive action (14). This report of an exploratory statistical analysis from the Collaborative Program on the Psychobiology of Depression of the Clinical Research Branch, National Institute of Mental Health (NIMH), attempts to increase information available for discriminating the patient at high risk of suicide from others in a high-risk group. We hope thus to contribute to the clinician's effectiveness in preventing suicide.

One previous approach to research in the clinical prediction of suicide has been to study the characteristics of patients who have made suicide attempts. On

Received May 21, 1984; revised May 16, 1986; accepted June 30, 1986. From the Department of Psychiatry, Rush-Presbyterian-St. Luke's Medical Center, Chicago; and the Department of Psychiatry, University of Iowa, Iowa City. Address reprint requests to Dr. Fawcett, 1720 West Polk St., Chicago, IL 60612.

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the basis of the assumption that the risk of suicide is associated with past suicide attempts, researchers have compared patients studied after suicide attempts with depressed patients who have not attempted suicide on a variety of psychological variables. Using this method, one study (15) demonstrated a fourfold greater incidence of previous stressful events, such as "exits" (losses of relationships), among depressed patients who made suicide attempts than in those who had not. This was supported in a subsequent study (16) illustrating that suicide and serious attempts were strongly related to negative life events occurring within 1 year after hospital discharge. Other investigators (17) have shown higher levels of hopelessness in patients who had made suicide attempts than in a comparison group of depressed patients who had not. Beck et al. (18) found hopelessness, measured by the Beck Hopelessness Scale, to be significantly associated with suicide in prospectively followed patients after hospitalization for depression or suicide attempts.

All previous studies except the prospective studies of Beck et al. (18) and Motto et al. (19) share one major methodological problem: the appropriateness of the sample studied. Studying populations of patients who have made suicide attempts has the advantage of permitting assessment of the patient's direct report about what he or she felt or experienced. However, it has been suggested (20) that patients who make suicide attempts may not be identical to those who die from suicidal behavior. Although there may be an overlap between groups, follow-up studies suggest that those who commit suicide and those who survive suicide attempts represent different populations.

Retrospective studies of patients who died from suicide eliminate this objection and provide a means for delineating the characteristics of patients who have completed and not just attempted suicide. Retrospective studies of cases of completed suicide have provided the core of clinical correlates of suicide that has been the basis of clinical teachings concerning the patient at risk for suicide (1-4). However, these retrospective studies necessarily suffer from several major limitations. They cannot describe the psychopathology as completely as a prospective effort can. Most important, they cannot generate a true control group (such as depressed individuals who do not commit suicide) to distinguish between those features associated with suicide and those associated with the presence of an affective disorder. Studies of completed suicides have relied on retrospective accumulation of unstandardized information, raising the possibility of memory distortion, inaccurate or incomplete information, and bias through selective attention and knowledge of the suicide. Moreover, findings from many studies currently available to us may not be as applicable today because of changing cohort effects with time, such as increasing frequencies of suicide among younger patients.

Improved clinical prediction will probably depend on a selective matrix of factors, some of which may

change with time under certain conditions (e.g., relationships, substance abuse, and severity of clinical features). Thus, a more focused profile of features emerging during the patient's clinical course may alert the clinician to a period of high suicidal risk. The present study was designed to assess a comprehensive range of demographic, clinical, and family variables collected by standardized methods in a prospective sample of patients who were at risk for suicide by virtue of the presence of affective illness. This study reports on the demographic and clinical features of 25 patients who committed suicide compared with the rest of the sample (929 patients), all of whom met the criteria for major affective disorder and were followed in the Collaborative Program on the Psychobiology of Depression (21). We attempt to discriminate features that might indicate high suicidal risk by comparing a large sample of patients with major affective disorder with a subsample drawn from the same population who committed suicide during follow-up. It is important to emphasize that this study examines the relationship of clinical features and suicide in a group of patients preselected on the basis of a Research Diagnostic Criteria (RDC) diagnosis of major affective disorder (21), whereas many other studies report on suicide in patients across the full spectrum of psychiatric diagnoses.

METHOD

The Collaborative Program on the Psychobiology of Depression involved the recruitment of 954 patients at five different academic medical centers for a descriptive nosologic, family, and follow-up study of major affective disorder diagnosed by RDC, beginning in 1977 (22). The sample was stratified: 599 patients with unipolar depression, 175 with bipolar type I affective disorder, 92 with bipolar type II affective disorder, and 88 with schizoaffective disorder were included after each agreed to participate in the study. These patients agreed to undergo lengthy diagnostic interviews on admission to the study and subsequent follow-up interviews at 6-month intervals for 4 years to record their clinical and treatment status. The data obtained summarized the patients' past clinical course, current clinical symptoms, current social functioning, and sociodemographic background at the time of admission to the study, soon after admission to treatment. Seven hundred sixty-three (80%) of the subjects were inpatients. Schedule for Affective Disorders and Schizophrenia (SADS) (23) interviews were conducted by clinical raters (psychiatrists, psychologists, social workers) trained to administer this interview and to arrive at reliable ratings of both historical and clinical features, using patient interview material as well as any additional data from charts or records. Interrater reliability on key clinical rating items in the SADS format has long been found to be high across raters in the five research centers (24-26). The study design

TABLE 1. Continuous Variables Associated With Suicide in a 4-Year Prospective Study of Patients With Major Affective Disorder

Variable	SADS Score						Analysis	
	Patients Who Committed Suicide (N=25)		Patients Who Did Not Commit Suicide (N=929)		t	df		p
	Mean	SD	Mean	SD				
Hopelessness	4.6	0.7	4.0	1.3	4.58	28.73	.001	
Loss of pleasure or interest	5.4	1.0	4.5	1.6	4.07	27.21	.001	
Fewer previous episodes of major affective disorder	2.0	1.2	3.2	3.7	3.41	19.11	.003	
Nonreactivity	5.0	0.9	4.4	1.5	3.19	23.06	.004	
Fewer adolescent friendships according to history	3.6	1.0	3.0	1.0	2.87	952	.004	
Depressed appearance	3.7	1.0	3.0	1.2	2.67	952	.008	
Social withdrawal	4.3	1.1	3.7	1.6	2.80	26.64	.009	
Diminished concentration	4.6	1.0	4.1	1.4	2.70	26.78	.01	
Indecisiveness	3.8	1.4	3.1	1.5	2.32	952	.02	
Alcohol abuse during index episode	2.3	1.4	1.8	1.4	2.16	952	.03	

allows for comparison of the 25 patients who committed suicide during the follow-up period with the surviving control group across all the standardized variables.

The determination of the outcome "death by suicide" was left to each center and was based on coroners' reports and clinical data available to clinicians familiar with the patient. In most cases of death by suicide, coroners' decisions verified the classification. Because the study was descriptive and took place in five different university medical centers, treatment was uncontrolled and not assigned randomly, varying from center to center and patient to patient. It should be kept in mind that the study does *not* achieve an epidemiologic sample; no attempt was made to select a representative or random sample of patients with affective disorder. In fact, some subcategories of diagnosis were stratified in the sample to provide sufficient numbers for comparisons (e.g., schizoaffective disorder, bipolar affective disorder). It is recognized that the sample of completed suicides is relatively small, which may limit the degree to which the findings of this study can be generalized to other clinical populations.

This report presents data covering a follow-up at 6-month intervals for a mean of 4 years after admission to the study. At each follow-up point, the status of at least 95% of the sample eligible and available for follow-up was determined. Two statistical procedures were used in the analysis of these data. Differences between patients who had or had not committed suicide in terms of continuous or "quasi"-continuous rating scale data (e.g., SADS severity ratings varying from 1 to 6) were analyzed by using Student's *t* statistic. Differences between patients who had or had not committed suicide in terms of dichotomous outcome variables (i.e., presence or absence of a symptom) were analyzed by using Fisher's exact test.

A critical concern in the interpretation of these results stems from the problem of multiple comparisons. In the present study we compared patients who committed suicide with the entire group of patients with major affective disorder in terms of 121 criterion

variables (i.e., symptoms). In the light of this, the chance of false-positive results is inflated beyond the .05 level required for the test of a single hypothesis. We have estimated that the true probability level for a 5% false-positive rate is at least $p < .005$, based on the Bonferroni inequality ($p = [1 - \alpha]^n$, where α is the original false-positive rate and n is the number of comparisons) (27). Therefore, results that are significant at the .05 or .01 level should be interpreted as only exploratory trends. Conversely, results that are significant at the $p < .005$ level may be used for inferential purposes. The reader should note that the analysis of these data is considered exploratory in nature owing to the large number of comparisons made and the relatively few a priori hypotheses tested. The prospective design limits the number of patients who completed suicide available for comparison with the surviving patients.

RESULTS

Eight (32%) of 25 suicides occurred within 6 months of entry into the study, and 13 (52%) of 25 suicides occurred during the first year of follow-up.

The tables illustrate significant differences between the suicide and surviving subgroups. Table 1 lists all of the variables that showed remarkable differences between the suicide group and the surviving sample according to *t* test. Table 2 lists all of the variables that differentiated the two groups according to Fisher exact test. The statistical test used was determined by whether the item was on a 6-point graduated scale (*t* test) or was dichotomous (Fisher exact test).

Four clinical features tested by *t* test discriminated significantly ($p < .005$) between the suicide and the control groups: hopelessness, loss of pleasure or interest, fewer previous episodes of major affective disorder in the suicide group, and loss of reactivity. A history of fewer adolescent friendships also discriminated the suicide group ($p < .004$). Mood cycling during the index episode (a change from a manic to depressive syndrome or vice versa) discriminated the suicide

TABLE 2. Dichotomous Variables Associated With Suicide in a 4-Year Prospective Study of Patients With Major Affective Disorder

Variable	Patients Who Committed Suicide (N=25)	Patients Who Did Not Commit Suicide (N=929)	χ^2 (df=1)	p
Depressive turmoil	4	9	30.5	.000
Delusions of thought insertion	3	13	10.78	.001
Mood cycling during index episode	10	146	8.80	.003
Delusions of mind reading	4	41	4.92	.03
Delusions of grandeur	7	102	5.39	.02
Not living with a child under 18	23	643	4.96	.03
Reduced major role status	14	305 ^a	5.70	.02
Dissatisfaction with life	20	473 ^a	6.29	.009
Drug abuse history	3	73	6.19	.03

^aData available for only 921 patients.

patients from the others by Fisher exact tests ($p < .002$). Although certain other items clearly discriminated significantly, their base rate was very low (i.e., present in three to four suicide completers). These items included depressive turmoil ($p < .000$), defined in the SADS as "rapid shifts from one dysphoric state to another, without the persistence of one affect," and delusions of thought insertion ($p < .001$).

Table 1 illustrates other features differentiating the suicide group obtained by *t* test, such as depressed appearance, social withdrawal, diminished concentration, indecisiveness, and alcohol abuse during the index episode. Table 2 lists additional features that suggest trends in the suicide group according to Fisher exact test, including *not* living with a child under 18 years of age, delusions of mind reading, delusions of grandeur, reduced major role status, dissatisfaction with life, and drug abuse history.

Diagnostic categories or subtypes such as bipolar I and II, unipolar, psychotic, endogenous, and primary or secondary did not differentiate the two groups, leaving cycling of mood during the index episode (implying a bipolar or schizoaffective diagnosis) the only affective subtype significantly associated with a suicidal outcome ($p < .002$). This was particularly true in men (seven of the 14 men who committed suicide).

The mean age of the patients who committed suicide did not differ from that of survivors. The patients who committed suicide were younger than those reported by earlier studies, however; their combined mean age was 39 years (women, 44.6 years; men, 35.5 years), and half of the suicides occurred in patients 30 years old or younger. Although the rate of suicide in men was greater, the difference was not significant in this sample. There was a minimal trend ($p < .06$) toward a higher rate of suicide in the never-married group than in the general sample, but there was no overrepresentation of suicide in the divorced or widowed.

Four hundred sixty-three (49%) of the entire sample of 954 patients gave a history of suicide attempts. Seventeen (4%) of these 463 patients died of suicide. Of the 491 patients with no previous history of suicide attempts, eight (2%) died of suicide ($\chi^2 = 3.15$, $df = 1$, $p = .08$). Thus, although 68% of the 25 patients who died from suicide had a positive history of suicide

attempts, 32% had no history of suicidal behavior. During the index episode there was no significant difference in frequency of suicide attempts between those who committed suicide (36%) and those who did not commit suicide (26%). There was no difference in medical lethality of previous attempts or suicidal ideation at intake. Of eight suicides that occurred within 6 months of admission to the study, five patients were rated at entry as having mild or no suicidal ideation by a trained clinical interviewer, two of the remaining three patients had made a medically serious attempt just before admission to the study, and one had made a moderately serious attempt. At entry, life stress as rated by the patient and the clinical rater did not correlate with a suicidal outcome in this sample.

DISCUSSION

The finding of a very high rate of suicide during the 6–12 months after entry into the study agrees with the findings of several previous studies. Roy (16) reported that 65% of suicides in his diagnostically heterogeneous sample of 94 patients occurred within 6 months of hospital discharge. Programs designed to reduce suicide rates might use clinical resources most effectively by developing more intensive follow-up and support systems for patients showing features of high risk over the first year after hospital discharge. Clinicians treating patients with depression who have recently been discharged from the hospital should be especially alert to a greater danger of suicide during the first posthospital year.

The age of suicide victims in this sample was younger than that noted in previous samples; 56% of the 25 suicides were 30 years old or younger at the time of the suicide. This is a notably higher rate of youthful suicides compared with earlier studies.

Several clinical features appeared to discriminate the patients who committed suicide from the control group, showing strong enough differences to be of possible value to the clinician. More intense hopelessness reported on admission to the study characterized the suicide group ($p < .001$). This observation emerged as a strong discriminator from a large number of

clinician-rated variables, and similar findings by Beck et al. (18) were based on self-report Hopelessness Scale scores. Complete or near total loss of interest and pleasure was another variable that significantly discriminated the suicide group from the control group of patients with major affective disorder ($p < .001$). That this finding discriminated suicidal patients may be somewhat unexpected, since loss of interest and pleasure is known to be a common symptom in depressive illness. In a previous report studying the capacity for pleasure as measured by a self-rating instrument constructed for this purpose in hospitalized psychiatric patients with major depressive disorders (28), it was found that a significant difference from control samples in the capacity for pleasure as measured by the Fawcett-Clark Pleasure Scale was present in only from 12% to 20% of the sample. In a large sample of patients with major depression (17), the capacity for pleasure correlated significantly (negatively) only with severity of depression and hopelessness as measured by the Beck Hopelessness Scale. These results may relate to the present findings in that both hopelessness and loss of the capacity for pleasure were the two most significant factors in discriminating the completed suicide group. The emergence of more severe ratings of nonreactivity (implying the loss of a capacity to react to positive events) as significantly associated with the patients who committed suicide ($p < .004$) is consistent with the finding of loss of interest and pleasure.

Another clinical characteristic that emerged as a potent discriminator between the suicide group and the reference group was the SADS item of depressive turmoil. Depressive turmoil also had a low base rate, occurring in only four of the 25 suicide patients. However, its presence may be an important predictor because it occurred in a total of only 13 of the entire sample of 954 patients with major affective disorder on admission to the study. That is a suicide rate of 31% in the patients with evidence of depressive turmoil ($p < .000$).

Characteristics suggesting psychotic thinking traditionally associated with schizophrenia, such as delusions of thought insertion and delusions of grandeur, emerged as associated with suicide in our affectively ill sample. However, these characteristics were present in only three and two, respectively, of the 25 suicide patients (these patients were diagnosed as having schizoaffective disorder by RDC). Even though schizoaffective or psychotic features were not significantly associated with suicide in the sample, when present these two symptoms (seen in patients with schizoaffective disorder) appeared to be correlated with suicidal outcome. Although the two characteristics of delusions of thought insertion and depressive turmoil were present in a minority of the patients who committed suicide, they stand out as clinical characteristics that, when present, might be of great importance to the clinician. The association between a history of mood cycling in the index episode and subsequent suicide was evident in 10 (40%) of the 25 suicides (seven of the 14 men, or

50%), which was significantly more frequent than in the control group ($p < .002$). This feature, considered with the others, would seem useful in discriminating the patients at high risk, especially in the light of the finding that RDC diagnoses of bipolar and schizoaffective disorder were not particularly associated with a suicidal outcome in this sample. The trend for ratings of delusions of grandeur to be present more often in patients who committed suicide ($p < .01$) may fit with the more severe mania observed in patients who have cycles of mood within episodes. The finding that patients who committed suicide had fewer previous episodes of major affective disorder (fewer than three episodes) agrees with the findings of Robins et al. (1). Perhaps the risk decreases with more episodes because of some accommodation to the state by a patient or a realization on the basis of experience that improvement is possible.

Trends toward greater dissatisfaction with life, social withdrawal, alcohol abuse, drug abuse, and loss of work role function were all clinically consistent but not strongly significant correlates in this sample.

Factors such as social withdrawal and a history of fewer adolescent friendships point to possible interpersonal deficits associated with suicide, as observed previously in a clinical situation by Fawcett et al. (29). The trend toward an association between committing suicide and not living with a child younger than 18 years old is consistent with reports by Veevers (30) and suggests a protective effect of the presence of a child. Marital status failed to predict higher suicide risk in this sample.

Suicide is probably a behavioral outcome reached through several different behavioral pathways and contingencies; no single set of individual clinical features observed at a single point in time would be expected to be a good predictor. This study suggests some features that, when observed prospectively under standardized conditions at the time of admission to the study in a population of patients with major affective disorder, correlated significantly with suicide as an outcome. These features may help the clinician to focus on features relevant to suicidal outcome from among the many signs and symptoms associated with major depression. Although it would be unrealistic to expect a single set of clinical features to accurately predict suicide, a serial assessment of these more highly suicide-correlated clinical features might help to alert the clinician to a time of high suicide risk during the course of illness. The absence of some clinical features traditionally associated with high suicide risk in the suicidal patients studied (such as previous suicidal behavior) should not lead the clinician to be complacent in managing a patient, and the knowledge of unavoidable limitations and biases that can affect any study should restrain us from discounting the clinical value of other traditional "predictors" depending on the individual clinical situation. Further statistical analyses of characteristics of the patients who committed suicide, using multivariate techniques to further test

and extend these exploratory findings, are now being conducted in an attempt to define combinations of features that may serve as more discriminating profiles for the clinician.

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Frequency and Presentation of Depressive Symptoms in Patients With Primary Degenerative Dementia

Lawrence W. Lazarus, M.D., Nancy Newton, Ph.D.,
Bertram Cohler, Ph.D., Jary Lesser, M.D., and Craig Schweon, Ph.D.

The authors examined the frequency and severity of depressive symptoms in elderly patients with presumed primary degenerative dementia and identified the signs and symptoms that provide a reliable basis for diagnosing depression. Forty-four patients and 42 control subjects were interviewed and rated on the Hamilton Rating Scale for Depression and the Sandoz Clinical Assessment-Geriatric Scale. Nine of the patients demonstrated symptoms suggestive of mild, four of moderate, and five of severe depression. Patients had significantly higher scores than control subjects on items that assess intrapsychic rather than vegetative symptoms of depression. These findings underline the importance of maintaining a high index of suspicion for concomitant depressive symptoms in patients with primary degenerative dementia.

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Significant depression and dementia have been found to coexist in elderly patients (1, 2). Estimates of the prevalence of clinical depression among patients with primary degenerative dementia (sometimes referred to as senile dementia of the Alzheimer type) have varied from 15% (3) to 30% (4) to 57% (5). Reifler et al. (6), studying cognitively impaired elderly outpatients, found that 33% with mild brain impairment met Research Diagnostic Criteria (RDC) for major depressive disorder. Miller (7), comparing elderly patients with demonstrated cognitive impairment from a variety of causes with normal control subjects, found that the demented group's mean score on the Hamilton Rating Scale for Depression fell in the mild to moderately depressed range.

Received March 28, 1985; revised Jan. 31 and April 28, 1986; accepted June 3, 1986. From Rush-Presbyterian-St. Luke's Medical Center, Chicago. Address reprint requests to Dr. Lazarus, Rush-Presbyterian-St. Luke's Medical Center, 1725 West Harrison St., Chicago, IL 60612.

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Knesevich et al. (8) examined the extent of depression in rigorously evaluated patients with the presumptive diagnosis of senile dementia of the Alzheimer type. In contrast to the studies described above, Knesevich et al. did not find that patients with senile dementia of the Alzheimer type who had mild cognitive impairment had evidence of depression compared with normal control subjects. Although the demented and control groups obtained mean Hamilton ratings in the nondepressed range, Knesevich et al. also found that the mean Hamilton scores of the patients with senile dementia of the Alzheimer type were higher than those of the control subjects. They attributed this difference to significant between-group differences on the Hamilton items that assess impairment in work and daily activities.

These conflicting reports about the prevalence of depression in patients with primary degenerative dementia and other dementing illnesses may reflect interstudy differences in patient selection and in the criteria used for diagnosing dementia and depression. For example, the terminology formerly used for classifying the different dementias has varied among different medical specialties and between investigators, thus making interstudy comparisons problematic. Alzheimer's disease, which is a neuropathological diagnosis accounting for approximately 60% of the chronic dementing illnesses at autopsy, is not a recognized diagnosis in *DSM-III*. It is also difficult to study a population of patients with a definitive diagnosis of primary degenerative dementia because certainty regarding the diagnosis can be established only at autopsy.

Another major problem accounting for differences in the estimates of concomitant depression in demented patients is the similarity of signs and symptoms in both illnesses and the difficulty of ascertaining what signs and symptoms are specifically related to depression and what signs and symptoms are specifically related to dementia. Patients with dementia and/or depression may present with similar vegetative (endogenous) symptoms, such as psychomotor retardation, weight loss, fatigue, decreased libido, and insomnia (7). The overlap of symptoms in dementia and depression may account for elevated depression rating scale scores in patients with primary degenerative dementia,

leading to an overestimate of the extent of depression in demented patients.

Because of the occurrence of vegetative symptoms in both primary degenerative dementia and depression, these rating scale items may not provide an accurate basis for estimating the frequency and severity of depressive symptoms in demented patients. It would be helpful, therefore, to identify specific signs and symptoms uniquely characteristic of depression in patients with primary degenerative dementia. Miller (7), observing that many demented patients display what appears to be genuine depressive affect in addition to somatic and behavioral symptoms of depression, suggested that clinicians can make a more accurate diagnosis of concomitant depression in demented patients by paying particular attention to a patient's mood in addition to noting vegetative symptoms.

One objective of the present investigation was to study the frequency and severity of depressive symptoms among elderly patients with a presumptive diagnosis of primary degenerative dementia compared with normal, age-matched, community-dwelling control subjects. We used the *DSM-III* classification of primary degenerative dementia (which refers to the senile and presenile dementias, the most common of which is Alzheimer's disease) to classify the cognitively impaired elderly patients who were studied. The second objective was to identify the specific depressive symptoms in patients with primary degenerative dementia to ascertain whether there are specific signs and symptoms that provide a reliable basis for accurately diagnosing concomitant depression.

METHOD

This study was conducted during the initial phase of a 5-year longitudinal study of the natural course of primary degenerative dementia undertaken at Rush-Presbyterian-St. Luke's Medical Center in Chicago. Patients with mild to moderate cognitive impairment with a presumptive diagnosis of primary degenerative dementia were referred to the research project from senior citizen centers, physicians, and hospitals in the greater Chicago area. All patients were living in their own homes in the community; none was institutionalized. Age-matched normal control subjects were healthy volunteers from the community who were paid for their participation. No subject had a history of psychiatric illness. All patients and a family member and control subjects consented to participation in the study after its nature had been explained to them.

All cognitively impaired subjects received a thorough medical, neurological, and psychiatric examination; CAT scan; EEG; and a battery of neuropsychological and laboratory tests to exclude patients who had reversible causes of dementia (9). Although a definitive diagnosis of primary degenerative dementia must await post-mortem confirmation, patients were included in the current study if there was 1) a detailed

history obtained from a responsible family member compatible with primary degenerative dementia, 2) no evidence of focal brain lesion, major systemic illness, major psychiatric disorder, or other cause of the dementing illness, and 3) laboratory and neuropsychological tests supporting the diagnosis.

Each subject was seen for a 45-minute structured interview conducted by two Board-certified psychiatrists (L.W.L. and J.L.) specializing in geriatric psychiatry. The interview included a mental status examination and a discussion of the subject's life style, daily activities, psychological and physical complaints, and recent and current mood. The two interviewers were sensitive both to the tendency of demented patients to minimize and/or deny the presence and severity of their cognitive and mood impairment and to how the patients' cognitive impairment could influence their response to questions needed to complete the Hamilton Rating Scale for Depression (10) and the Sandoz Clinical Assessment-Geriatric Scale (11). Thus, the interviewers rated patients on the basis of their non-verbal as well as their verbal responses during the interview. Following the interview, the psychiatrists independently rated each subject on the 24-item Hamilton scale and the Sandoz scale. (The Hamilton scale was used because it is an observer-rated rather than a self-rating scale and because of its extensive use in the study of depression and demonstrated validity in assessment of extent and nature of depressive symptoms [12].) Satisfactory interrater reliability was achieved for each measure (for the Hamilton scale, $r=.68$, $p<.01$, and for the Sandoz scale, $r=.92$, $p<.01$).

To compare the patients and control subjects on Hamilton scale scores and Sandoz scale scores, a two-way analysis of variance was used, covarying for education (table 1). To compare the two groups on the individual items of the Hamilton scale, t tests were used (table 2).

RESULTS

Forty-four patients (17 men and 27 women) with primary degenerative dementia (mean \pm SD age = 67.34 ± 8.02 years) and 42 age-matched control subjects (18 men and 24 women; mean \pm SD age = 69.48 ± 7.01) were rated on the Hamilton scale. Forty-six patients (19 men and 27 women) and 43 control subjects (19 men and 24 women) were given the Sandoz scale. Despite attempts to match the patients and control subjects as closely as possible, significant differences were found between the two groups in level of education: the patients had a mean of 11.67 ± 3.02 years of education versus 12.50 ± 3.02 years in the control group ($F=8.36$, $df=1,96$, $p<.005$). Education was used as a covariate in the data analysis to control for this group difference. There are slight differences across items of the two rating scales used to assess patient and control groups; therefore, the numbers and degrees of freedom vary in tables 1 and 2.

TABLE 1. Depression and Confusion Scores of Patients With Primary Degenerative Dementia and Normal Control Subjects

Item	Hamilton Rating Scale for Depression				Sandoz Clinical Assessment-Geriatric Scale							
	Score				Confusion Subscale				Depression Subscale			
	N	Mean	SD	F	N	Mean	SD	F	N	Mean	SD	F
Group												
Patients with degenerative dementia												
Men	17	8.71	5.97		19	12.21	6.34		19	30.74	7.39	
Women	27	13.37	8.35		27	16.15	7.04		27	38.59	13.51	
Control subjects												
Men	18	5.39	3.85		19	5.26	3.86		19	21.05	5.40	
Women	24	6.42	5.50		24	4.21	3.51		24	20.75	5.38	
Analysis of variance												
Group				12.60 ^{a,b}				64.75 ^{b,c}				47.99 ^{b,d}
Sex				4.90 ^{a,e}				0.94 ^c				2.76 ^d
Group by Sex interaction				2.12 ^a				4.44 ^{c,e}				3.90 ^d

^adf=1, 80.^bp<.001.^cdf=1, 83.^ddf=1, 84.^ep<.05.

To provide a measure of the extent of cognitive impairment and to separate those symptoms associated with depression, the Sandoz scale was operationally divided in the data analysis into two subscales reflecting the two separate components assessed by this scale. One of the subscales was the confusion subscale, which consisted of the four Sandoz scale items that assess degree of confusion, mental alertness, impairment of recent memory, and orientation. Ratings on these four items reflected subjects' responses on the mental status examination as well as the raters' observations of subjects' cognitive functioning throughout the interview. The remaining 14 Sandoz scale items assess mood disturbance, somatic complaints, and behavioral symptoms usually related to depression. Scores on these items were combined to form the Sandoz depression subscale.

As would be expected, patients with primary degenerative dementia were rated as significantly more cognitively impaired than the control subjects on the Sandoz confusion subscale. Within the patient and control groups, Sandoz confusion subscale scores did not correlate with age or years of education, so these two factors were not considered further in the analyses. However, there was a significant sex by group interaction: the female patients were rated as more cognitively impaired than were the male patients (table 1).

The patients were also rated as demonstrating significantly more depressive symptoms than control subjects on both the Hamilton scale and the Sandoz depression subscale (table 1). Since a Hamilton score greater than 18 is the usual criterion for including depressed inpatients in antidepressant drug trials, we selected a total score of 23 or greater on the Hamilton

scale as indicative of a severe degree of depressive symptoms, a score of 17 to 22 as indicative of moderate symptoms, and a score of 12 to 16 as indicative of mild depressive symptoms. According to these criteria, nine (20%) of the 44 patients demonstrated symptoms suggestive of mild depression, four (9%) of moderate depression, and five (11%) of severe depression. In contrast, only three (7%) of the 42 control subjects fell into the mild and two (5%) into the moderate depression range. None of the control subjects fell into the severe depression range. In summary, 18 (40%) of the patients with primary degenerative dementia, compared with five (12%) of the control subjects, exhibited evidence of at least mild depression. As would be expected if the Hamilton scale and the Sandoz depression subscale were measuring similar depressive symptoms, there was a significant positive correlation between ratings on these scales ($r=.73$, $N=86$, $p<.001$). There was a significant effect of sex on the Hamilton scale: female subjects scored significantly higher (were more depressed) than male subjects (table 1).

Within the group of patients with primary degenerative dementia, the correlation between scores on the Hamilton scale and the Sandoz confusion subscale was nonsignificant ($r=.10$), indicating that there was no relationship between degree of cognitive impairment and extent of depressive symptoms. Level of education and age also did not correlate with the level of depressive symptoms in either the patients or the control subjects.

To determine what symptoms of depression predominate in primary degenerative dementia, an item analysis of the Hamilton scale was done. Significant differences were found between the patients and con-

TABLE 2. Scores on Items of the Hamilton Rating Scale for Depression of 44 Patients With Primary Degenerative Dementia and 42 Normal Control Subjects

Hamilton Item	Patients With Primary Degenerative Dementia		Control Subjects		Comparison		
	Mean	SD	Mean	SD	t	df	p
Depressed mood	1.23	1.15	0.50	0.63	3.59	84	<.001
Feelings of guilt	0.23	0.56	0.29	0.50	-0.50	84	n.s.
Suicide	0.05	0.21	0.02	0.15	0.54	84	n.s.
Insomnia, early	0.30	0.59	0.57	0.66	-2.00	84	<.05
Insomnia, middle	0.25	0.61	0.41	0.62	-1.16	84	n.s.
Insomnia, late	0.30	0.55	0.33	0.56	-0.31	84	n.s.
Work and activities	1.77	1.15	0.38	0.49	7.19	84	<.001
Psychomotor retardation	0.50	0.72	0.09	0.29	3.33	84	.01
Agitation	0.23	0.42	0.10	0.29	1.66	84	n.s.
Anxiety, psychic	1.59	1.15	0.91	0.87	3.07	84	<.01
Anxiety, somatic ^a	0.77	0.67	0.50	0.59	1.98	84	<.05
Somatic symptoms (gastrointestinal) ^a	0.21	0.46	0.07	0.26	1.64	84	n.s.
Somatic symptoms (general)	0.66	0.77	0.45	0.66	1.32	84	n.s.
Genital symptoms ^b	0.19	0.40	0.32	0.53	-1.07	60	n.s.
Hypochondriasis	0.11	0.32	0.05	0.31	0.97	84	n.s.
Loss of weight ^c	0.36	0.71	0.12	0.40	1.90	83	n.s.
Insight ^d	0.56	0.86	0.27	0.62	1.02	50	n.s.
Diurnal variation, a.m. ^e	0.14	0.41	0.07	0.26	0.87	82	n.s.
Diurnal variation, p.m. ^e	0.16	0.43	0.05	0.22	1.51	82	n.s.
Depersonalization and derealization	0.09	0.36	0.10	0.37	-0.06	84	n.s.
Paranoid symptoms	0.16	0.42	0.00	0.00	2.41	84	<.05
Obsessive-compulsive symptoms	0.05	0.21	0.29	0.55	-2.68	84	<.01
Helplessness ^a	0.71	0.84	0.14	0.35	3.96	84	<.001
Hopelessness ^b	0.52	0.72	0.14	0.35	3.04	84	<.01
Worthlessness	0.55	0.66	0.10	0.29	4.03	84	<.001

^aFemale control subjects scored significantly higher on this item than did male control subjects ($F=6.48$, $df=1,81$, $p=.013$).

^b31 patients and 31 control subjects were rated on this item.

^cSignificant sex by group interaction: female patients and male control subjects scored higher than male patients and female control subjects, respectively ($F=1.74$, $df=1,80$, $p=.024$); 41 control subjects were rated on this item.

^d41 patients and 11 control subjects were rated on this item.

^e43 patients and 41 control subjects were rated on this item; diurnal variation, a.m. and p.m., make up one Hamilton item.

control subjects on 11 of the 24 items of the Hamilton scale (table 2). Significant elevations in the group of patients with primary degenerative dementia were found on the Hamilton items that assess signs and symptoms reflecting inner feeling states of depression and despair, rather than somatic or vegetative symptoms of depression. For example, depressed mood, anxiety, and feelings of helplessness, hopelessness, and worthlessness were significantly greater in the patients than in the control subjects. These symptoms reflect disturbance in self-perception, mood, and future outlook that are characteristic of inner feelings of depression and that may, in these patients, constitute a depressive reaction secondary to some awareness of cognitive decline.

In contrast to expressions of an internal state of depression, the patients did not score significantly higher than control subjects on the majority of items assessing vegetative symptoms, such as sleep disturbance, weight loss, and insomnia. However, the patients had higher scores on the item assessing difficulty carrying out work and daily activities and the item assessing psychomotor retardation. This is not surprising in that such vegetative symptoms reflect behavioral and somatic impairments characteristic of both dementia and depression.

DISCUSSION

Our results suggest that patients with a presumptive diagnosis of primary degenerative dementia have a significantly higher frequency of depressive symptoms than age-matched normal control subjects. Hamilton scores fell within the mildly to severely depressed range in 40% of the patients with primary degenerative dementia, compared with 12% of the control subjects. These results suggest a high frequency of concomitant depressive symptoms in elderly patients with a presumptive diagnosis of primary degenerative dementia who are referred for neurological evaluation. Furthermore, it underlines the importance of providing a careful psychiatric assessment of patients referred for cognitive assessment so that concomitant depression can be identified and treated.

These results confirm the findings of several previous studies (4-6) that found depression to be a prevalent, concomitant problem in patients suffering from a dementing illness such as primary degenerative dementia. We found the frequency and severity of depressive symptoms to be somewhat less than that found by Reifler et al. (6) and Miller (7), which may reflect interstudy sampling differences. Reifler et al. and Miller studied demented patients who were referred for psy-

chiatric evaluation, whereas we studied patients with a presumptive diagnosis of primary degenerative dementia who were residing in the community and who had no psychiatric history; they were referred for assessment of cognitive impairment. Whereas Reifler et al. and Miller studied patients with a variety of dementing illnesses, we studied a population with a presumptive diagnosis of primary degenerative dementia.

The second objective of our investigation was to ascertain the specific symptoms that may characterize depression in patients with presumed primary degenerative dementia to aid clinicians in the often difficult task of accurately diagnosing concomitant depression. Two conclusions emerge from our results. The primary degenerative dementia and control groups differed significantly on many items of the Hamilton scale that are reflective of an intrapsychic state of depression, such as depressed mood, anxiety, and feelings of helplessness, hopelessness, and worthlessness. Similar to Miller's observations (7), many of the patients in this study appeared to demonstrate genuine depressive affect and expressed, verbally and/or nonverbally, feelings of low self-esteem, helplessness, and hopelessness.

In contrast, the patients with primary degenerative dementia scored significantly higher on only two vegetative, or endogenous, items of the Hamilton scale (impairment in work and daily activities and psychomotor retardation) that reflect behavioral changes associated with either dementia or depression. The presence of impairment in work and daily activities and psychomotor retardation in a demented patient would not necessarily imply that the patient had a concomitant depression. High scores on Hamilton items assessing such vegetative (endogenous) symptoms may contribute to a high total Hamilton score, which could inadvertently mislead the clinician into overdiagnosing depression in demented patients.

Several clinical implications derive from our study. Clinicians working with patients with Alzheimer's disease and other dementias need to maintain a high index of suspicion for concomitant depression. Greater importance might be placed on endogenous or vegetative symptoms, since the former may be more reliable

discriminators of depression in these patients. Appropriate treatment of a demented patient's concomitant depression may offer the demented patient and his or her family some hope for improvement in mood and the quality of remaining life. Mood and behavioral rating scales that capture the intrapsychic manifestations of depression in the elderly may be useful adjuncts to the serial psychiatric interview in clarifying these diagnostic dilemmas. Research is needed to clarify the changes in mood that occur during the progressive stages of Alzheimer's disease and other dementing illnesses and the efficacy of psychopharmacological and other treatment approaches for the demented, depressed patient.

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Loss of Vision Due to Central Serous Chorioretinopathy Following Psychological Stress

Gary S. Gelber, M.D., and Howard Schatz, M.D.

The authors studied 33 patients with central serous chorioretinopathy and found that a very disturbing psychological event had preceded the loss of vision in 91% of the cases. The acute disturbance preceded the first visual symptoms by an average of 7 days. When relapses occurred, the psychological disturbances were often less severe and preceded the visual symptoms by minutes or hours. In some cases vision improved 1 to 2 weeks after the patient learned of the amelioration of the original distressing situation. The majority of the patients were found to be tension ridden, and 48% had cardiovascular abnormalities.

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Central serous chorioretinopathy is an eye disorder of unknown etiology in which vision is reduced because of a detachment of the sensory retina of the macula, the area of most acute vision. Central serous chorioretinopathy is the most common cause of retinal detachment of the macula in patients under the age of 50. The loss of vision is due to changes that are clinically observable by ophthalmological examination. It is not a hysterical visual loss.

The sensory retinal detachment is caused by leakage of serous fluid from the capillary layer of the choroid through a break in the retinal pigment epithelium (figure 1). The serous fluid then collects between the retinal pigment epithelium and the rods and cones, causing a sensory retinal detachment that can be documented by fundus fluorescein angiography. Visual field examination usually reveals a relative scotoma in the area corresponding to the detachment.

Central serous chorioretinopathy accounts for approximately 5% of the patients referred to retina specialists. It is nine times more likely to occur in males

than in females (1). Patients with this condition are usually 30 to 50 years of age. It is bilateral at onset in approximately 5% of the cases. The leakage of fluid generally occurs for a few weeks to many months, and in approximately 80% of the patients (2) the retina reattaches and good vision returns.

In a report of one case by Lipowski and Kiriakos (3), a woman developed central serous chorioretinopathy immediately after she discovered her husband having coitus with his niece. Another psychiatric study (4) reported tension and displeasure in two patients with this disorder. Ophthalmologists (5-8) have recorded states of tension and distress in their patients with central serous chorioretinopathy and have remarked anecdotally that such patients are "antsy," "annoyingly insistent," and "hard driving."

Our hypotheses at the initiation of this study were that 1) there might be specific personality factors common to patients with central serous chorioretinopathy and 2) events involving the eyes in some manner (for example, viewing a very disturbing event) might have preceded the onset of visual symptoms.

METHOD

Thirty-five patients were interviewed by a psychiatrist (G.S.G.) after the diagnosis of central serous chorioretinopathy had been made with fluorescein angiography by a retinal specialist (H.S.). All patients consented to participating in a research study that would be published with their identities disguised. Two patients who could not accurately remember the period before the onset of their visual loss were eliminated from our starting group of 35 patients.

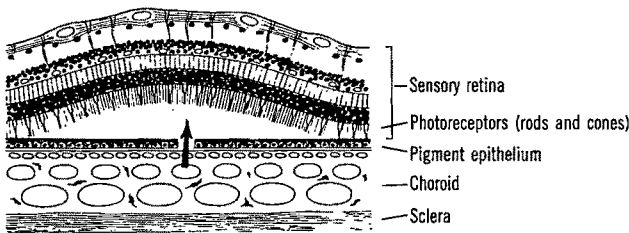
The age range of the 33 patients was 25-62 years (mean, 38 years) at the onset of central serous chorioretinopathy; 20 patients (61%) were between 35 and 45 years of age. Four were women and 29 were men. There were 28 Caucasians, three Malayo-Polynesians, and two East Indians. Sixteen were married, nine were divorced (three remarried, six not remarried), and eight had never married. Thirteen of the patients were from the middle and lower socioeconomic classes, and the remaining 20 patients were from the upper middle class. Two were psychiatrists. Ten subjects were undergoing job or career changes at the time of their

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FIGURE 1. Retinal Detachment Due to Leakage of Fluid From Choroid Through Break in Pigment Epithelium (arrow) Into Subretinal Space



attack, and four held two or more jobs simultaneously. Three of the men were homosexual.

The patients were interviewed for an average of 2.9 hours (range, 1–20 hours). The structured section of the interview covered 32 topics and dealt with issues such as personality factors and the onset of symptoms. To avoid suggesting to the patients that a distressing event might have preceded their visual loss, we did not inquire about specific events or distressing experiences. Instead, we requested, in as nonsuggestive a manner as possible, that the patients describe the month or two before their loss of vision. We then asked them to describe the worst crisis they had ever experienced in their lives. After this, the patients rated the period before their visual symptoms on a 0–100 scale, with 100 representing the worst crisis of their lives. By asking the patients themselves to rate the period before their visual loss, we hoped to elicit the subjective importance—and perhaps idiosyncratic significance—that a premorbid event might have. We then asked for the next worst crisis and allowed them to change their rank ordering. This was done to help them remember other crises and to reduce the chance that the severity of the crisis preceding the visual symptoms had been distorted by the symptoms themselves. The patients were also asked to rate their usual daily level of psychological distress using the same scale. We converted the 0–100 scale to ratings of mild, moderate, and severe.

Using the test devised by Friedman and Powell (9) to diagnose type A behavior, we used the patients' biographical material and their behavioral and psychomotor responses to score their time urgency, competitiveness, and hostility. The nonstructured section of the interview included open-ended questions—for example, dealing with the patients' previous experiences of distress.

RESULTS

Emotional Intensity Immediately Before Visual Symptoms

Thirty of the patients (91%) had undergone a very distressing experience during the hours or weeks pre-

TABLE 1. Distress Levels Experienced Usually and Before Visual Loss in 33 Patients With Central Serous Chorioretinopathy

Usual Daily Distress Level	Distress Level Before Visual Loss					
	Mild		Moderate		Severe	
	N	%	N	%	N	%
Mild	0	0	1	3	18	55
Moderate	0	0	2	6	2	6
Severe	0	0	0	0	10	30

ceding their first attack of central serous chorioretinopathy. Table 1 compares the patients' reports of distress immediately before their visual loss with their usual levels of distress.

Case 1. Mr. A, a 32-year-old handyman, developed central serous chorioretinopathy 8 hours after his girlfriend told him that she was "going to run off and become a whore." He recounted, "I just flipped . . . I cried . . . Then I argued reasonably and the problem was settled the next day, but I was left with the eye problem." He rated this crisis as the worst he had ever experienced, "worse even than when my father killed himself." He said that the incident was totally unexpected. His condition worsened four times over the next 4 years; two of these attacks followed psychological distress. The remaining two relapses occurred when he was not feeling any conscious psychological distress but had been using cocaine, a few hours before in one case and 24 hours before in the other.

Case 2. Mr. B, a 41-year-old Samoan carpenter, had been "happily married" but lost the vision in one eye 48 hours after his wife spent the night out. He felt certain his wife had engaged in sexual activity with another man. His rage and jealousy were extreme; he said the experience was the worst he had ever lived through. He said that his wife's behavior was totally unexpected.

The following case is presented as an example of a crisis that was not the most intense of the patient's life.

Case 3. Dr. C, a 34-year-old married physician, became involved with a woman he had known as a young man, "the love of my life." During a blissful trip he pledged that he would get a divorce and marry her, and she encouraged him. She then wrote him that she had decided never to see him again. Shocked and grief stricken, he wept bitterly and began losing the vision in one eye 8 to 9 days later, without any other significant events intervening. He rated this shock as "severe" (his daily level of distress was "moderate"). The worst crisis of his life had occurred when their relationship had ended 10 years previously.

Temporal Course of Psychological Disturbance

Eleven patients (33%) had each experienced a single psychological crisis that began abruptly and reached full intensity within minutes to hours. Central serous chorioretinopathy then developed an average of 7 days after the onset of the acute crisis (range, 8 hours to 14 days). There was an inverse correlation between the intensity of the distress and the amount of time that

elapsed before visual loss; it developed after a shorter interval in the majority of patients who experienced the most intense crises.

Some cases of central serous chorioretinopathy were preceded by a series of crises, as in the following.

Case 4. Mr. D, a 35-year-old journalist, was imprisoned in Lebanon and threatened with torture 2½ months before the onset of central serous chorioretinopathy. He knew there was a possibility he would be killed. He was released after 1 week and returned to the United States, where, 2 months before the onset of his visual symptoms, he ended his relationships with both of his girlfriends. Thirteen days before his loss of vision his aged father had an artificial lens implanted in his eye. Because his father had had major difficulties with anesthetics, Mr. D feared that his father would die. Three days before his visual loss he snorted cocaine. He characterized this entire 2½-month period as the worst of his entire life.

Another set of patients had been extremely tense for years before their visual symptoms began, and when they experienced a crisis their distress responses exacerbated their underlying tension.

Personality Traits of Patients With Central Serous Chorioretinopathy

We found the following personality traits with great frequency during the clinical interviews: perfectionism and high performance requirements, intense nervousness, worrying, time urgency, extreme hard work, dauntless struggle against adversity, competitiveness, and hostility. (Hostility may be illustrated by the example of a patient who, when angered by his wife's new furniture arrangement, tore a large rug out of his living room, knocking over the furniture. We rated a busy chief executive officer of a large corporation perfectionistic because, for example, he ironed all his shirts himself "to get them to look just right.")

Twenty-three patients (70%) revealed an inability to use social supports; increases in distress often led them to communicate less—a "pressure cooker" effect. Psychosomatic problems (colitis, ulcer, migraine, and other headaches) were present in eight (24%); blood pressure and cardiac problems, which are dealt with later, were found in 16 (48%). Easily aroused physiological activation (e.g., diarrhea, weight loss, hyperventilation) during periods of stress was present in 18 patients (55%). There was an unusual sign: four patients (12%) were already standing up in the waiting room when the examiner came out to ask them in. We suspect this reaction may have been due to impatience and nervousness.

Using the structured interview for determining type A behavior, we found that our patients had an average score of 29, compared with the 28 found by Friedman and Powell (9) in 1,012 patients who had had myocardial infarctions. Of their subjects, 90% scored 13.41 or higher; 97% of our patients had a score of 13.41 or higher. The average score found by Friedman and Powell in type B individuals was 5.5.

TABLE 2. Types of Crisis-Provoking Situations Experienced by 33 Patients Before Onset of Central Serous Chorioretinopathy

Type of Situation	N	%
Crisis at work	11	33
Work crisis plus concomitant failure of love relationship	7	21
Marital crisis or loss of lover	6	18
Conflicts over children	3	9
Conflicts with parents	2	6
Fear of death of a parent	2	6
Death of a parent	1	3
Sports tournament	1	3

Types of Crisis-Provoking Situations

Situations of amatory distress frequently preceded the onset of central serous chorioretinopathy (table 2); 14 patients (42%) were in anger-provoking situations shortly before the onset of their visual symptoms. With the exception of Mr. D, who learned that his father was to have an eye operation, there were no distressing events that implicated the eyes in a real or symbolic sense.

Recurrences and Ameliorations

Recurrences of central serous chorioretinopathy were experienced by 15 patients (45%) and followed new psychological disturbances by only several minutes to 3 days. The psychological disturbances were only moderately intense when compared with the severe distresses that had preceded the initial crises. Ameliorations of vision occurred within 1 to 2 weeks after improvement of the original crisis situations.

Case 3 continued. Dr. C's vision deteriorated further over the following 2 weeks to the extent that he lost his ability to see at night. At this point he called his mistress and proposed once again. Even though she did not accept his proposal, she did agree to see him in another 2 weeks. He felt "exalted," and 7 days after the phone call he noticed that he was able to read his clock radio at night for the first time since he had lost his night vision. An ophthalmological examination the following day confirmed the amelioration.

Three months passed, during which the relationship deepened and his eye improved steadily. Then, one morning 4 months after the original onset, they had a "stormy" interaction on the phone. He wept after the call. The next day he noted for the first time in 2 months a spot in his field of vision, and that evening he realized that he had again lost the ability to read his clock radio at night.

Cardiovascular Findings

A history of cardiovascular problems was present in 16 patients (48%). Twelve (36%) had high blood pressure (systolic pressure ≥ 150 mm Hg or diastolic pressure ≥ 90 mm Hg [10]), five (15%) had palpitations, four (12%) had heart murmurs, two (6%) had abnormal ECGs, and one (3%) suffered from angina pectoris. Five patients (15%) had two or more of these problems. The average age at onset of central serous

chorioretinopathy in this subgroup of patients with cardiovascular findings was 41.5 years. To our knowledge, a high prevalence of cardiovascular findings has not been previously reported in central serous chorioretinopathy.

Additional vascular findings were migraine headaches in four patients (12%) and Raynaud's disease in two (6%). Three patients (9%) suffered from gout; two of them had developed gout and begun taking medication shortly before the onset of their visual symptoms.

The following did not appear to be significant factors in the onset of central serous chorioretinopathy: experiencing subjective feelings of rage or tension in the region of the eyes ($N=1$, 3%), seeing a psychologically traumatic sight ($N=1$, 3%), overprotection of eyes during childhood ($N=1$, 3%), or crying ($N=3$, 9%). There was no correlation between eye, hand, or leg dominance and the side on which central serous chorioretinopathy occurred. There were no cases of ocular tics, blepharospasm, use of birth control pills, or hysterical personality. Four patients (12%) expressed sad affect while recounting the crises that had preceded their visual symptoms.

DISCUSSION

This investigation is, to our knowledge, the first psychiatric study in the English language of a series of patients with central serous chorioretinopathy.

In those patients who experienced severe psychological crises before the onset of the visual symptoms, central serous chorioretinopathy occurred even in the absence of preexisting high blood pressure and tension-engendering personality traits. On the other hand, in patients who had high blood pressure or tension-producing personality traits, central serous chorioretinopathy sometimes followed only moderate distress.

The fact that 36% of the patients had high blood pressure (compared with 12.2%–14.6% of the general American population aged 35–44 years [10]) suggests that retinal choroid capillaries, or a sphincter leading to them, may be chronically weakened by increased blood pressure and/or overwhelmed by blood pressure spikes. Increased intravascular pressure could cause the breaks in the retinal pigment epithelium (figure 1, arrow) and the leakage of serous fluid that characterize the histopathology of central serous chorioretinopathy. It is possible that blood pressure spikes occur in some normotensive individuals during successive episodes of stress, long before the clinical appearance of central serous chorioretinopathy. This hypothesis is supported by experiments in which daily intravenous injections of epinephrine in two types of monkeys produced retinal lesions closely resembling those of central serous chorioretinopathy (11).

The individuals who develop central serous chorioretinopathy may have a constitutionally determined chorioretinal susceptibility to it. We do not believe that

central serous chorioretinopathy is a direct result of the personality traits themselves. The personality traits increase the severity of the individual's daily tensions, emotional distress, and physiologic arousal, and these in turn may set in motion retinal vascular and blood pressure changes that predispose the individual to central serous chorioretinopathy.

Cocaine use, to our knowledge not previously reported in studies of central serous chorioretinopathy, preceded the only relapses in our series in which there was no premorbid psychological stress (case 1). The two patients (cases 1 and 4) who used cocaine developed bilateral central serous chorioretinopathy, which is less common than unilateral, after each episode of use. This suggests that inhalation through the nostrils could damage retinal choroidal vessels bilaterally through angiotoxic mechanisms and/or by acute increases in blood pressure.

Although some retrospective exaggeration of the severity of the crises preceding the visual symptoms may have occurred, many patients did not make a causal connection between the crises and their eye problems.

Only four patients (12%) demonstrated sad affect during their interviews. The absence of depressive symptoms after a major crisis and the individual's dauntless struggle to overcome adversity were striking personality features of this group of patients. Many felt they could handle their problems themselves: "You're talking to the captain. How can you recommend psychotherapy to me?" said one patient.

Of the 33 patients, only one experienced a "visual perception of a psychologically traumatic sight" that could conceivably be "causally related to pathophysiological change" (3), and one other patient (case 4) developed central serous chorioretinopathy after his father's eye was operated on (but also after a series of psychological traumas and cocaine use). Thus, the eye's role in seeing a traumatic sight or as a locus for symbolic expression or for punishment (as in the Oedipus myth) was not a significant part of the histories of 31 (94%) of our patients.

Although the crises preceding visual loss had different themes (unrequited love, separation fears, work), for each of the patients the particular theme had a specific, calamitous meaning that cut at the Achilles heel of his or her emotional life. For example, of the seven patients (21%) who developed central serous chorioretinopathy after being rejected by their loved ones, four had suffered traumatic childhood separations from one or both parents, and the other three patients were highly sensitive to loss because of other life experiences.

Because of the short interval between the psychological disturbance and the appearance of visual symptoms, the premorbid stress could be identified. The visual changes and retinal leaks could be measured by the ophthalmologist. Under these circumstances the physician's reliance on the patient's subjective evaluation of the evolution and intensity of the condition is

greatly reduced. Therefore, in central serous chorioretinopathy the pupil of the eye can be a window through which we can observe a psychosomatic disorder.

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Reactivation of Combat-Related Posttraumatic Stress Disorder

Zahava Solomon, Ph.D., Ronald Garb, M.D., Avraham Bleich, M.D.,
and Daniel Grupper, M.D.

The authors conducted an exploratory study of the nature and course of reactivation of combat-related posttraumatic stress disorder. Experienced psychiatrists, they each independently assessed 35 men with recurrent combat-related posttraumatic stress disorder. Two major types of reactivated posttraumatic stress disorder, each representing a different degree of pathology, were delineated: uncomplicated reactivation and heightened vulnerability. The second category was further subdivided into specific sensitivity, moderate generalized sensitivity, and severe generalized sensitivity. The authors conclude that reactivation of war-related trauma is a complex phenomenon that may take different forms.

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Combat stress has long been documented as a cause of psychiatric disorder (1-3). Of the variety of enduring combat-related stress syndromes (4), the most prevalent is posttraumatic stress disorder. This relatively recently named syndrome (DSM-III) may appear in an acute form, differentiated into its characteristic clinical symptoms within 6 months of the traumatic event, or it may take the form of chronic or delayed posttraumatic stress disorder. Chronic posttraumatic stress disorder is diagnosed when the symptoms persist for longer than 6 months. Delayed posttraumatic stress disorder is diagnosed when the symptoms appear for the first time after a period of at least 6 months and without apparent antecedent warning symptoms. In this study we focus on a unique variety of posttraumatic stress disorder: reactivated combat-related posttraumatic stress disorder. Here, a previous combat stress reaction, a specific form of acute posttraumatic stress disorder, is again precipitated after exposure to similar stress.

Reactivation of stress disorder may occur in a variety of stressful life events. Silver and Wortman (5), in an extensive review, contended that traumatic experiences often render the afflicted individual vulnerable in the face of future adversity. Even in situations where the individual appears to have overcome the trauma, heightened vulnerability may ensue.

Lindemann (6) noted that a former unresolved grief reaction may be reactivated when the bereaved is reminded of his or her loss. The precipitating factor for the delayed reaction may be a deliberate recall of circumstances surrounding the death, or it may be an incident in the patient's life. Similar observations were made by Weiner et al. (7) regarding recurrent anniversary grief reactions generated by stimuli reminiscent of the original loss. Women who have been raped also evidence similar reactivation of their response to the original trauma (8).

Although the phenomenon of reactivated response to trauma has been documented in both the military and the civilian realms, empirical research pertaining to recurrent combat-related posttraumatic stress disorder is rather limited. Christenson et al. (9) suggested that losses associated with the patient's age, such as parental loss, children leaving home, impending retirement, and increasing medical disability, serve as triggers activating and unmasking latent war-related posttraumatic stress disorders. Interestingly, these authors found that latent posttraumatic stress disorder symptoms such as nightmares about World War II had been dormant in their patients for many years. This observation is consistent with an earlier 20-year follow-up study of World War II veterans (10) in which war-related posttraumatic stress disorder symptoms became evident as the veterans got older.

An earlier study by our group (4) conducted during the 1982 Lebanon War found a very limited number of reactivated combat stress reactions. As time passed, however, many more cases came to our attention. To our knowledge, reactivation of combat-related posttraumatic stress disorder following exposure to a new combat experience as a clinical category has never been singled out for investigation. The unfortunate reality of Israel's military situation, with frequent wars and repeated exposure of Israeli men to combat, presents a unique opportunity for the study of reactivation.

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vated combat-related posttraumatic stress disorder. Even when spared the rigors of combat, Israeli men are regularly exposed to military stimuli that serve as continuous reminders of their combat experience. After 3 years of mandatory active military service, all Israeli men up to the age of 55 serve in the reserves for about 30 days a year.

In the present study, 35 case histories of veterans with recurrent combat-related posttraumatic stress disorder were reviewed to explore the nature and course of this reactivation.

METHOD

We each carefully reviewed the medical files of Israeli soldiers diagnosed as suffering from combat-related posttraumatic stress disorder during or immediately after the 1982 Lebanon War. Experienced psychiatrists, we recognized 35 of these soldiers as suffering from recurrent combat-related posttraumatic stress disorder. The files were compiled on the basis of thorough psychiatric evaluations conducted for diagnostic purposes preliminary to the soldiers' receiving psychiatric treatment at the central mental health clinic of the Israel Defense Forces. The files included clinical evaluations and verbal accounts of therapy sessions. We individually reviewed each of the medical files of the 35 men in order to establish the psychiatric diagnosis of reactivated or exacerbated posttraumatic stress disorder.

First, using *DSM-III* criteria, we confirmed the examining clinician's diagnosis of posttraumatic stress disorder. Then, we determined whether the 35 cases represented first-time occurrences or a reactivation or exacerbation of symptoms. The eligibility criteria were either the reactivation of a completely dormant or resolved episode of combat stress reaction from the 1973 Yom Kippur War or the exacerbation of residual symptoms of combat stress reaction that were present between the 1973 Yom Kippur War and the 1982 Lebanon War.

In most cases we agreed in our assessments. In the few cases where we had initially reached somewhat different conclusions, we reached agreement after discussion. Our diagnoses of posttraumatic stress disorder were checked against computerized military records. These records contain the combat history and a somatic and psychiatric medical history of every soldier. The availability of this information minimizes the possibility of mistaken or factitious reports of earlier combat stress reactions.

All 35 patients were soldiers on reserve duty. Their ages ranged from 28 to 39 years (median = 31 years). Thirty-three (94%) of the soldiers were married, one was divorced, and one was single. All of the soldiers demonstrated a high motivation to serve in the army despite having had a combat stress reaction, which would have permitted them to receive a military discharge had they desired it.

RESULTS

Assessment of charts revealed a spectrum of symptoms ranging in intensity of severity from very mild to extreme behavioral and functional disability. Two major groups of combat-related reactivated posttraumatic stress disorder were delineated, representing degrees or stages of the clinical picture of the disorder. The second major group was subdivided into three subgroups. The resulting four groups represent different points on the spectrum of pathology to recovery that is part of the natural history of combat-related posttraumatic stress disorder (4). These stages do not necessarily imply a stepwise course of recovery or deterioration but, rather, serve as an index of adaptability and containment or, on the contrary, measure the degree to which coping has failed.

Uncomplicated Reactivation

Eight (23%) of the 35 soldiers experienced uncomplicated reactivation of posttraumatic stress disorder. These individuals demonstrated the highest degree of functioning after having suffered an earlier combat stress reaction. This patient population consisted of soldiers who had either been diagnosed as having a combat stress reaction as such or had suffered from an immediate, undiagnosed combat stress syndrome. Subsequently, they seemed to have completely recovered from the effects of their traumatic experiences and were symptom free. On call-up to the 1982 Lebanon War, however, they developed full-blown posttraumatic stress disorder after being exposed to a battle situation.

Case 1. This 28-year-old kibbutz member was married and the father of one child. He had been in regular service with the armored division in the 1973 war. His battalion participated in intense battles and suffered many casualties. He had volunteered to rescue wounded comrades under direct fire at great personal risk; he ceased only after sustaining a mild injury. After resuming his combatant role following medical treatment, he was the only one to escape alive when a grenade was thrown into his armored personnel carrier. Following this traumatic incident he developed combat stress reaction. He was referred for psychiatric treatment, and his military profile (the Israel Defense Forces physical and mental fitness rating that indicates the soldier's ability to function militarily) was temporarily lowered. With treatment, his symptoms receded and his military fitness rating was increased at his request. Between the wars he trained with his new unit, functioned well, and established good social ties with both peers and commanders. He was also successful in his personal life. He married a fellow member of his kibbutz, completed studies in electronics, and was satisfactorily employed in his new profession.

When the 1982 Lebanon War broke out, he was mobilized with his battalion and functioned adequately. During combat, however, the convoy in which he was riding was ambushed and his armored personnel carrier sustained a direct hit. This event closely resembled his experience in the 1973 war, and, as he put it, "It aroused what was dormant inside of me for 9 whole years." The patient reacted with

depressed mood, loss of appetite, irritability, concentration problems, and sleep disturbances. When the distressing symptoms became unbearable, he turned to his battalion surgeon for help.

Heightened Vulnerability

The second major category of recurrent posttraumatic stress disorder included 27 soldiers whose first episode of combat stress reaction left a residual of stress, rendering them more vulnerable to further episodes. The degree of this heightened vulnerability varied considerably. Some soldiers were apparently able to resume their premorbid level of functioning in all spheres of life; their increased sensitivity was confined to certain military stimuli exclusively. In others, a more generalized sensitivity developed to stimuli far removed from the original trauma. Finally, a more chronic impairment in both civilian and military functioning following the 1973 combat stress reaction was evidenced. Each of these subcategories is illustrated here by a brief clinical example.

Specific sensitivity. Eighteen (51%) of the 35 soldiers, despite persistent minor and diffuse symptoms resulting from the 1973 war, succeeded in their overall professional and social functioning. They also did well during their occasional uneventful periods of reserve duty, despite a rise in their tension level. However, these men demonstrated a specific sensitivity in that specific stimuli reminiscent of the original trauma retained the power to reactivate the disorder. When these men encountered stimuli directly related to the original trauma, the intensity of their posttraumatic stress disorder symptoms increased. Specifically, during their reserve service, these soldiers often exhibited stress-related symptoms such as hypersensitivity to noise (particularly weapons), reduced appetite, diarrhea, and increased anxiety. These distressing symptoms, however, did not severely impede their performance. These soldiers had invested much effort in coping, predominantly using the mechanisms of denial and repression to enable them to function adequately. Their heightened sensitivity to specific military stimuli, however, became more apparent when the Lebanon War broke out in 1982. Most of the soldiers in this group reacted with high anticipatory anxiety on receiving the order to report to active service. After they were mobilized and entered the military domain, they responded with exacerbated stress to relatively minor events that reminded them of their earlier traumatic experiences. In many of these instances, reactivation of a residual or subthreshold posttraumatic stress disorder to full-blown posttraumatic stress disorder occurred without any substantial combat exposure.

Case 2. This 27-year-old self-employed man was married and the father of three children. He had done his regular service in 1973, when he was caught up in the Yom Kippur War. Following intense battle exposure he developed combat stress reaction. For a period of several months both his military and his civilian functioning were severely impaired.

Gradual improvement was noted, and the occurrence of nightmares and intrusive recollections of the war was reduced to approximately once a month. He was able to rehabilitate his personal life: he married and went into private business with much success.

Although his civilian functioning appeared to be unimpaired, specific sensitivity was noted to military settings during his annual reserve duty. During his reserve service between the 1973 and 1982 wars, he felt anxious and depressed and was somewhat withdrawn, although he did not disclose his feelings to his peers. In fact, he maintained adequate military functioning and demonstrated high motivation to continue to serve in the army. As a result, his military fitness rating was raised.

When called up for the 1982 Lebanon War, however, he was flooded with anxiety. He was bothered by nightmares and suffered from nocturnal enuresis. During the daytime he was also very fearful and, as he put it, "frightened to death." He would not part with his helmet. Nonetheless, he did not request release from his duties, which he continued to fulfill adequately. He sought psychiatric treatment only after the cease-fire came into effect.

Moderate generalized sensitivity. The original sensitization of three (9%) of the 35 soldiers had generalized. These men displayed an acute stress reaction to stimuli that were only remotely related or apparently totally unrelated to the original trauma. As a consequence, they experienced a high degree of suffering that permeated many areas of their lives. Symptoms of posttraumatic stress disorder were apparent in civilian settings, and these symptoms increased in military atmospheres. These men reported sleep disturbances, nightmares, anxiety, irritability, and uncontrollable outbursts of anger. They tried in various ways to avoid dealing with situations that aroused acute anxiety, but they were not very successful in reducing their anxiety. To attain mastery, some of them used phobic mechanisms, and others reported using alcohol and drugs. Their symptoms were accompanied by some impairment of functioning in both civilian and military settings. Yet, despite their generalized sensitivity, these men continued to serve in the reserves. When the orders for the 1982 war were issued, they experienced intense anticipatory anxiety that severely hindered their capacity as combatants. Some of them reacted with a full-blown syndrome following minor military stimuli and were discharged without entering the battlefield or participating in actual battles.

Case 3. This 36-year-old tank crewman was married and had three children. He had been engaged in heavy battles during the 1973 Yom Kippur War; his unit suffered many casualties. When riding in an armored personnel carrier, he witnessed the gruesome death of his commander and several close friends. Subsequently, he developed a dissociative reaction that later crystallized into chronic posttraumatic stress disorder. The stress symptoms that persisted included sleep disturbances, nightmares, intrusive thoughts, and depressed mood. Between 1973 and 1982 he gradually improved, and the frequency and intensity of posttraumatic stress disorder symptoms declined somewhat. Despite his distress, the patient refused psychiatric treatment and was reluctant to share his feelings with his peers. At his own

initiative, his military fitness rating was restored to its prewar level, and he resumed membership in his original unit in the reserve forces. In the 9-year period between the wars he was constantly troubled by debilitating symptoms of posttraumatic stress disorder, yet he maintained a limited but acceptable level of functioning in both civilian and military settings. Exacerbation of symptoms occurred during his periodic reserve duty, evidenced by severe anxiety, sleep disturbances, markedly reduced appetite, and recurrent flashbacks to scenes he had witnessed in the 1973 war. The patient reported that during these periods of reserve duty he was haunted by the fear that something horrible was about to happen and that it would result in his death. Somehow, however, he continued to do reserve service.

When mobilized for the 1982 war, he reacted with severe anticipatory anxiety and marked intensification of posttraumatic stress disorder symptoms. Most prevalent were intrusive recollections of his experiences in the 1973 war. Although he did not take part in active combat and was stationed near the front but not at it, he exhibited a full-blown stress reaction; his symptoms severely impaired his military functioning. At this point he sought help. He revealed in therapy that the scenes he had witnessed in 1973 were so horrible and shocking that they had haunted him ever since. He feared that they were indelible and would haunt him until he died.

Severe generalized sensitivity. Six (17%) of the 35 soldiers displayed more or less total inability to function in any setting; mobilization emphasized this global incapacity. The soldiers in this group were still listed (by oversight) on the army active roster. They were called up for but did not take part in combat in the 1982 Lebanon War. The arrival of the call-up note in the mail worsened their condition to such an extent that they experienced more or less immediate, severe, paralyzing anticipatory anxiety.

Case 4. This 33-year-old man was married and had one child. He had suffered constantly from nightmares, concentration difficulties, sensitivity to noise, and constant anxiety since serving in the Yom Kippur War. During the years his fears had widened: he began to fear terrorists, strangers, and dark places. He kept a gun in his home and would constantly search for shelter while walking down the street in case an emergency should arise. His fears always became more severe during reserve duty. He did not receive any treatment for his condition and tried to hide his symptoms, especially from his wife.

When he received his call-up for the 1982 Lebanon War, he suffered acute anxiety that became progressively more severe. Within less than a week of starting to serve his reserve duty, which did not entail actual combat, he asked to see the company physician and was sent to a mental health treatment facility. Here he was diagnosed as suffering from severe posttraumatic stress disorder, with symptoms of trembling, heavy perspiration, asthma, and depression. After initial preliminary treatment, he was released from duty and discharged as unfit for service.

DISCUSSION

Close scrutiny of our data clearly indicates that reactivation of war-related trauma is a complex phe-

nomenon that may take various forms. Two major groups, or degrees, of reactivated posttraumatic stress disorder were delineated. Uncomplicated or classical reactivation was assessed in eight (23%) of the 35 soldiers. These individuals appeared to have completely recovered from their first episode of combat stress reaction, were symptom free, and had resumed their full level of premorbid functioning in the period between the 1973 Yom Kippur War and the 1982 Lebanon War. Heightened vulnerability and exacerbation of residual posttraumatic stress disorder symptoms ensued in the majority of the sample—27 (77%) of the 35 soldiers—but the symptoms varied considerably in breadth and intensity. In this group, who seemed to have resumed their prewar level of functioning and seemed unaffected in all other spheres of life, 18 of the men showed specific sensitivity to military stimuli. In nine other men in this group, however, a deeper, more generalized sensitivity to stress was evident. This generalized sensitivity exerted a differential effect, somewhat debilitating three and severely incapacitating six. In these soldiers exacerbation of residual symptoms rather than reactivation of latent posttraumatic stress disorder was observed.

These data are consistent with earlier clinical evidence (5) suggesting that traumatic experiences scar the traumatized individuals, weakening their resilience to future stress. Furthermore, even when individuals seem to have resolved their reaction to trauma, heightened vulnerability that is easily reawakened often ensues. Our data indicate a considerable variability in the depth of this residual vulnerability. This vulnerability is most apparent in response to stimuli directly reminiscent of the original trauma, but it is not restricted to such stimuli. It appears that even when combat-related posttraumatic stress disorder remits or, on the other hand, persists and evolves into a more stable form, the afflicted person may become highly sensitized to stress in general. He is permanently altered, harboring the potential for a future response on reexposure to threatening stimuli (11).

The type and intensity of the later stressor that serves as a precipitating factor for the reactivated and/or exacerbated posttraumatic stress disorder deserves special attention. Our data clearly indicate that soldiers who had previously suffered from posttraumatic stress disorder may collapse years later even under relatively moderate combat stress. Furthermore, hypersensitivity to military stimuli, once established, may turn into more generalized sensitivity in many areas. This means that the development of a full-blown posttraumatic stress disorder may be induced by a wide range of less specific stimuli, such as life events completely unrelated to war. This observation is consistent with earlier observations of reactivated war trauma in U.S. veterans (9).

Psychiatric symptoms and impaired social functioning are two facets of residual posttraumatic symptoms that are often observed following exposure to extreme stress. Interestingly, although all of our subjects suf-

ferred from some stress-related symptoms, their level of functioning was generally impaired much less than their symptoms would lead one to expect. The 26 soldiers who experienced uncomplicated reactivation or specific sensitivity, who constituted 74% of the sample, reported no impairment in either civilian or military functioning. The nine soldiers with more generalized sensitivity exhibited considerable stress-related symptoms coupled with somewhat restricted functioning. Results indicate that residuals of combat stress are expressed mainly by psychiatric symptoms and to a lesser degree by impaired social functioning.

A pertinent issue with regard to prognosis is the role that repeated exposure to stress plays in recovery from posttraumatic stress disorder. There are two contradictory perspectives. The first contends that repeated stress strengthens the individual's coping and promotes resilience in the face of future adversity (12, 13). The second postulates that repeated stress results in depleted resources, rendering the individual more vulnerable when confronted with lesser stress (14). Of particular interest is the question of what effect repeated exposure to military stimuli has on casualties with combat-related posttraumatic stress disorder. Does it operate to extinguish the disorder, or does it retard recovery? The unfortunate reality for many Israelis entails considerable stress in the form of both frequent intense wars and sporadic terrorist activities. A sizable percentage of the male population not only participates in wars but also continues to serve in the active reserve. Unlike the discharged U.S. soldier, for example, who has little chance of being exposed to combat or other military conditions again, the Israeli soldier is frequently exposed to such stimuli. These circumstances allow for testing the validity of the two perspectives. Our data suggest that repeated sporadic exposure, especially periods of service in the reserve, reactivates latent memories of traumatic war experiences, delaying spontaneous recovery and impeding full recovery from posttraumatic stress disorder.

The residual stress reported by most of our subjects between wars was indicative of their vulnerability. It may be that the damages of early traumatic experiences had not been adequately treated. More than half of the afflicted soldiers in the sample who had been in treatment dropped out. In the majority of the cases reviewed here, there was evidence that the soldiers went to great lengths to hide their mental state from their commanders, comrades, friends, and even close family. Their symptoms were accompanied by feelings of shame, guilt, and lowered self-esteem. In Israel,

where the army is highly valued as a necessary means for survival, male identity is strongly linked to military functioning. Given this background, feelings of shame and guilt over debilitating residual symptoms of combat stress reaction are easily understood. It seems that the social norms and the resultant reluctance to admit to problems and seek professional help may be possible intervening variables that increase the risk for reactivation of posttraumatic stress disorder in this particular population.

In conclusion, we feel that the major contribution of this exploratory study is that it casts light for the first time on the reactivation of posttraumatic stress disorder during reexposure to combat. This study is only a first step in increasing our understanding of reactivation, its incidence, its course, and its correlates. More systematic longitudinal studies with adequate controls are called for.

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Expectations and Outcomes for Patients Given Mental Health Care or Spiritist Healing in Puerto Rico

Joan D. Koss, Ph.D.

In Puerto Rico, spiritism offers a traditional alternative to community mental health services. The author compares reported expectations and outcomes of mental health center patients and patients of spiritist healers. The spiritists' patients reported significantly higher expectations, especially for mood and feeling complaints. Both patient groups had a similar duration and severity of symptoms. The outcome ratings of spiritists' patients were significantly better than those of therapists', but this difference could be accounted for by the higher expectations of the spiritists' patients. With these exceptions, the findings do not account for the selection of one type of treatment over the other.

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Although a number of studies have described medical pluralism in Hispanic societies and among Hispanic groups in the United States, few have described how folk healing systems interrelate with mental health care or with patients' views of alternative health care in relation to a specific set of symptoms (1-8). Kleinman and Gale (9) compared outcome assessments of patients in Taiwan roughly matched for type of sickness and sociodemographic characteristics, and Salan and Maretzki (10) found that clients of healers in Indonesia had higher expectations of improvement if they had received previous treatment at biomedical health care facilities. This paper follows these studies in describing the experiences of patients in biomedical mental health care settings as contrasted with patients who went to traditional healers in Puerto Rico.

In this paper I compare how patients who received mental health care from therapists and those who received care from traditional healers initially viewed

their treatment with regard to a specific set of complaints and how they reported their expectations had been met by each type of health care provider. As in previous studies, no claim is made for the efficacy of either biomedical or traditional treatment. The assessment of efficacy is relative to how each system's practitioners and patients perceive symptoms and complaints and how they value different methods and modalities.

TRADITIONAL HEALING IN PUERTO RICO

Espiritismo is a syncretic religiophilosophical healing system. It originated in France through the writings of Leon H. Rivail (1803-1869), a scholar and teacher who published seven books and a journal under the nom de plume of Allan Kardec. Through his and his followers' proselyting efforts, these writings were widely disseminated in Spain, eastern Europe, and Latin America by the end of the nineteenth century (3, 4, 11).

In Puerto Rico, almost everyone knows "something" about spiritism. An estimated 60% of persons of all socioeconomic classes have visited a spiritist center at some time. Some of the 24 health professionals interviewed on this subject, including medical doctors, came from families of spiritist healers and carried out dual roles as both biomedical and spiritist healers.

A spiritist healing takes place most frequently in a group setting, and no fees are charged by those healers considered legitimate. Mediums receive spirit messages or become possessed by either good or molesting spirits in order to diagnose, counsel, prescribe herbal and ritual remedies, and prognosticate. Table 1 compares some general aspects of the treatment process in community mental health center (CMHC) outpatient psychotherapy and spiritist healing.

METHOD

Data were collected in the context of an experiment that had as its general objective to intensify and structure the interface between *Espiritismo* and the public health care system through both CMHC- and hospital-based clinical services (12). The specific goal was to promote a dialogue between traditional healers

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TABLE 1. Aspects of CMHC Outpatient Psychotherapy and Spiritist Healing^a

Aspect	Psychotherapy	Spiritism
Diagnostic process	Screening interview Patient describes problem Therapist listens to patient's explanations and complaints before making diagnosis	Spiritist observes patient Spiritist describes patient's difficulties Spiritist "captures" or "receives" patient's problems into his or her body through visions
Practitioner characteristics	Therapist usually of a higher social class than patient Therapist's role validated by education and professional status Therapist usually viewed as authoritative but readily cooperative and capable of misjudgment Therapist often a young adult man or woman (more women than men) Therapist viewed as knowledgeable but exhibits only limited empathy Therapist thought to be a normal, middle-class, educated person	Spiritist usually of same social class as patient Spiritist's role validated by special, often ecstatic, experiences Spiritist viewed as vehicle of divine authority, much more powerful than patient Spiritist usually an older woman (approximately three women to one man) Spiritist viewed as having special knowledge of spirits and unusual empathy Spiritist thought to have unusual, not normal, attributes
Treatment	Patient receives advice and/or psychotropic drugs as primary treatment as well as individual or group psychotherapy Focus of therapy on adaptation and amelioration of conflict; practical solutions suggested Therapist seldom works with family Therapist rarely discusses relevance of problems to general meaning of life	Patient receives valuable but not central advice; treatment consists of personal rituals (e.g., prayers) and exorcistic rites conducted by spiritist; herbal preparations sometimes used Changes in coping style insisted on; personal transformation of patient emphasized, possibly with goal of becoming a healer Spiritist almost always includes near or extended family in diagnosis and treatment, at least through patient All treatment deals with life and cosmologic meaning

^aModified version of a table in a previous publication (12).

and health professionals, as well as to compile information on healing practices within each system and on how both types of practitioners explained their concepts and methods to each other. Informed consent was obtained from all subjects after the nature of the study had been fully explained.

Twenty to 70 persons attended project meetings, over six different programs. Detailed information on personal and social characteristics, patient caseloads, treatment practices and styles, and attitudes and beliefs about each treatment system were gathered from 47 therapists and 49 spiritist practitioners. The spiritist participants were all recognized healers in their communities, having been presidents or core members of their healing groups for more than 5 years. The therapist group included experienced psychosocial technicians (with a bachelor's degree in any field), clinical psychologists (with a master's degree), social workers (with a bachelor's or a master's degree), nurses (licensed practical nurses and registered nurses), and two medical doctors. All of the therapists worked in community mental health programs of the Department of Health of Puerto Rico or in associated agencies such as Project Hope. Their mean age was 29 years (range=23–46 years). Spiritist healers had practiced their avocation longer: their mean age was 43 years (range=33–80 years).

Data presented here were derived from observations and interviews with patients of regular participants in the project's programs. Cases were chosen by interviewing the first new patient on a selected day or evening when a therapist or healer was providing his

or her usual services. The therapists' patients were drawn from three CMHCs and a psychiatric hospital, sampled from the caseloads of 31 of the 47 therapists participating in the study. The spiritists' patients were drawn from 16 *centros*, reported by 32 of the 49 participating spiritist healers. The study sample consisted of 100 patients and their therapists or spiritist healers: 46 of the subjects were therapists' patients and 54 were spiritists' patients.

Before receiving or providing treatment, the patients and their therapists rated the degree of problem resolution or symptom alleviation they expected on a scale of 1 (complete resolution or alleviation) to 5 (not at all resolved or alleviated).

After receiving treatment, 56 of the patients (24 therapists' patients and 32 spiritists' patients) rated the degree of problem resolution or symptom alleviation they experienced on the same scale they had used before treatment. The therapists and spiritist healers who treated these patients also completed this scale.

In the analysis, the patients' presenting complaints are categorized into types and analyzed as complaint profiles. Other variables studied included duration and severity of individual complaints.

RESULTS

Expectations of Healing

Data on expectations were analyzed to provide a comparative, descriptive perspective on mental health

services and spiritist healing practices in Puerto Rico rather than to relate expectations to outcome (13, 14). The questions addressed were, Do patients bring distinct types of expectations to each of these very different healing modalities? Is utilization of mental health care or traditional healing associated with different types, duration, or severity of presenting complaints? and If the presenting complaints of therapists' patients do not differ in type from those of spiritists' patients, do they differ in perceived intensity of their resolutions?

Discussions of traditional healing have repeatedly suggested that a division of labor underlies the documented simultaneous or consecutive use of biomedical and folk healing practices (3, 12, 15, 16). Finkler (17) described the complementarity of biomedicine and spiritualism in Mexico. The spiritists in Puerto Rico who participated in this study specified that some causes of illness or distress are "material" rather than "spiritual." Most patients who reported somatic complaints were initially referred to medical doctors, except when the complaint was seen as solely due to emotional distress or the patient had already been rejected by physicians. A healer who referred a patient to a physician usually retained responsibility and asked that the patient return to him or her to report the physician's diagnosis. Five of the 54 patients of spiritists sought such treatment following dissatisfaction with medical or psychiatric care; four used spiritist healing as an adjunct to medical treatment to deal with emotional distress; and three used it to satisfy their need for social explanations of the cause of their medically treated illness. This informal division of labor has existed for years and is an adaptation to past legal and social constraints (11).

Since community mental health services are relatively new in Puerto Rico, spiritism does not specify within its belief system referral of their patients to psychiatric care. One of the results of the Therapist-Spiritist Project was that some of the healers who participated began to identify "psychic causes" for their patients' problems and to refer the patients to mental health programs (12).

Demographics of the Patients

The spiritists' patients were younger: 21 (39%) were 21–30 years old, compared with two (4%) of the therapists' patients. Twenty-two (48%) of the therapists' patients were 31–50 years old; there were only 16 (30%) patients in this age group among the spiritists' patients. This may indicate greater use of spiritism by young adults encountering their first taste of life's difficulties, but that is not conclusively demonstrated. More men—28 (61%) of the 46 patients—saw therapists, and more women—30 (56%) of the 54 patients—saw spiritists; the difference was not significant. These observations do not quite agree with those of Harwood (3) for New York households, where significantly more women and older persons declared

themselves spiritists. These persons were probably adherents and healers rather than health seekers.

The two patient groups in this study were basically similar in occupational and socioeconomic status. Housewives were frequent patients of both spiritist centers and mental health clinics. One difference was the greater number of unemployed persons among the therapists' patients—11 (24%)—compared with spiritists' patients—three (6%). This was due to frequent use of community mental health services to obtain welfare or disability payments but also may have been due to the lowering of the social status of persons suffering chronic mental illness.

Comparison of Presenting Complaints

The primary presenting complaints of therapists' and spiritists' patients were similar. The most frequently mentioned complaints of therapists' patients were problems with children or marriage, nervousness, insomnia, hallucinations, and uncontrolled behavior. Spiritists' patients reported even more family problems, nervousness, and negatively toned visions but also reported headaches and backaches; they did not report as much insomnia or uncontrolled behavior.

The 166 different complaints reported were grouped into seven categories: social maladjustment, mood, thought, feeling, addiction, somatic, and behavioral. To examine frequencies of different types of complaints, each patient was given a score of 1 if he or she had at least one complaint in a particular area; otherwise the patient got a score of 0. These data were analyzed by a repeated-measures analysis of variance (ANOVA) in which the multivariate approach to repeated measures was used for assessing overall within-subject effects (18–20).

As shown in table 2, when the complaint categories were collapsed, the number of therapists' clients reporting a symptom in any category was nearly one-third greater than the number of spiritists' patients. Therapists' patients generally reported more symptoms than did spiritists' patients, perhaps because therapists attempted to elicit symptoms, while spiritists only reported to clients what they "captured" (from visions of spirits) and focused on illness causality rather than probing for complaints (table 1).

Not surprisingly, the frequency with which different categories of complaints were cited by patients differed significantly (multivariate $F=32.55$, $df=6,93$, $p<.001$). (All multivariate tests used Wilks's lambda criterion [21, 22].) Of special interest, the pattern of complaints differed significantly between the two groups of patients, as indicated by the interaction between symptom type and patient category (multivariate $F=4.04$, $df=6,93$, $p<.001$). Follow-up univariate tests were used to examine differences between spiritists' and therapists' patients on each type of complaint. With a Bonferroni adjustment to control the α level at .05 for the set of tests (18), therapists' patients were found to have significantly more feeling complaints. Differences

TABLE 2. Presenting Complaints of Therapists' Patients and Spiritists' Patients

Type of Presenting Complaint	Therapists' Patients (N=46)		Spiritists' Patients (N=54)		ANOVA	
	N	%	N	%	F (df=1, 98)	p
Social maladjustment	20	43	20	37	0.40	.517
Mood	27	59	18	33	6.76	.011
Thought	12	26	10	19	0.82	.368
Feeling	37	80	22	41	18.92	.000 ^a
Addiction	2	4	3	6	0.07	.785
Somatic	15	33	27	50	3.11	.081
Behavioral	6	13	5	9	0.36	.551
Any type of presenting complaint	13	28	20	37	10.26	.002

^aSignificant at .01 with Bonferroni adjustment (21).

between groups were not significant on other categories of symptoms, although there was a trend for therapists' clients to have more mood and fewer somatic complaints.

Garrison (16), observing 50 spiritists' clients at one *centro* in New York City, reported a similar distribution of complaint types, except that somatic complaints were less frequent among New York spiritists' clients (40% of her sample). She suggested that the "somatic" complaints reported were psychosomatic rather than organic and were likely to have been reported to a physician but discounted as indicating physical illness. This was also true in Puerto Rico. Garrison concluded that New York spiritists were "treating about the same types of thoughts, feelings and behaviors" as were mental health professionals (p. 156). This was corroborated in Puerto Rico with regard to thought and behavioral complaints (table 2); however, therapists' patients had significantly more feeling complaints.

Duration and Severity of Complaints

Duration of complaints was measured by time between the initial appearance of a specific symptom or complaint and the time the patient first sought treatment for that complaint. A 6-point scale consisted of intervals of less than 6 months, more than 6 months, and more than 1, 2, 3, and 5 years. A score of 1 was assigned to less than 6 months; a score of 6 denoted 5 years. The mean duration for both groups fell within the more than 2 years category. The difference between patient groups with regard to the relationship between duration of a patient's symptoms and selection of a healer or therapist was nonsignificant ($\chi^2=3.62$, $df=5$, $N=97$).

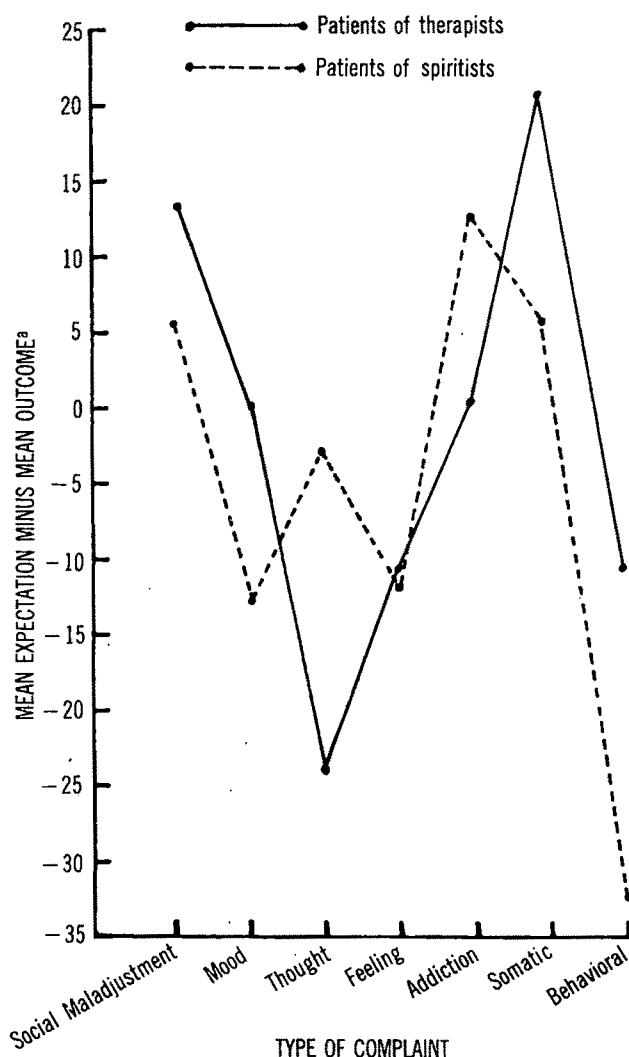
Severity of complaint was measured on a 4-point scale from 1=slight to 4=incapacitated. Ratings were based on patients' reports of severity and on the opinions of their therapist or spiritist healer. The difference between groups in the relationship between severity of a given patient's symptoms and treatment by a spiritist healer or a therapist was not significant ($\chi^2=5.40$, $df=3$, $N=98$), indicating no reliable difference.

Expectations and Outcome

There was a trend for spiritists' patients to have more favorable expectations regarding treatment of all types of complaints. Their mean rating was 2.02, compared with 2.57 for the therapists' patients. This difference was not significant ($F=3.10$, $df=1,54$, $.05 < p < .01$). For the 56 patients who rated outcome after receiving treatment, the ratings of the spiritists' patients were significantly more favorable than those of the therapists' patients: 1.85 versus 2.63 ($F=6.42$, $df=1,54$, $p < .05$). When expectation and outcome ratings were compared, however, there was virtually no difference between the two patient groups: the mean difference between expectation and outcome for spiritists' patients was 0.17 and that for therapists' patients was -0.06. Spiritists' patients might have started treatment with somewhat higher expectations and ended with more positive reports of outcome, but there was no difference in change in pre- and posttreatment ratings between therapists' and spiritists' patients.

With regard to differences in type of complaint and outcomes (figure 1), spiritist healers did better than expected and also somewhat better than did therapists on mood and behavioral complaints. Therapists did much better on thought complaints. Both did about equally well on feeling complaints. Spiritists did somewhat worse than expected on addiction and somatic complaints, but therapists did poorly on both mood and somatic complaints. These patterns could indicate a complementarity in choosing one type of treatment over the other. For example, spiritist clients seemed to expect and get more help with what were labeled behavioral problems, such as general poor health, excessive crying, and violent behavior, all of which could fall under the rubric of stress-related disorders. However, therapists also did better than expected with behavioral problems, although not as well as did spiritists. Both types of treatment, spiritists' and therapists', did more poorly than expected for patients with social maladjustment complaints, such as hypersensitivity to noise and people and financial problems. These analyses do not indicate a reason for a clear-cut division of labor.

FIGURE 1. Differences Between Expectancies and Outcomes for Presenting Complaints of Therapists' Patients and Spiritists' Patients



^a100-point scale; a higher, positive score indicates outcome worse than expected, and a low, negative score indicates outcome better than expected.

DISCUSSION

Therapists' and spiritists' patients presented slightly different complaint profiles to the practitioners they chose—more mood and feeling complaints were presented to therapists. Spiritists' patients had somewhat higher levels of expectation of improvement for different types of complaints when differences between expectation and outcome were compared. However, both groups quantitatively assessed the treatment effect in much the same way—they improved, stayed the same, or worsened to the same extent.

Given these findings, several concerns can be raised. The literature on expectations points to the need for an independent measure of outcome beyond that of patients' ratings if we want to demonstrate that positive

expectations lead to positive outcomes. The analysis reported here does not include independent measures by therapists and spiritist healers. In fact, therapists and spiritist healers reported higher expectations and outcomes than reported by their patients. This accords with studies that show little agreement between patients' expectations and therapists' assessed outcomes (23). It is further evidence for the general proposition of Kleinman (24) that there are important differences in implicit models for explaining a particular set of complaints used by health care professionals and by their patients.

Finkler (17) pointed to "restructuring the patient's perception" of his or her condition as leading to successful outcome in clients of traditional healers. Although patients with symptoms attributed to physical causes may seek to return to a premorbid state of feeling good and functioning adequately, persons seeking relief from emotional distress may have other priorities, such as improved functioning and more optimal feeling states. In this study, patients reported that they sought treatment for all of these reasons but focused on the goal of more optimal feeling states, regardless of alleviation of symptoms. This type of treatment goal may be associated with longer duration of complaints.

Given differences in the explanatory models used by patients and clinicians, their judgments about effectiveness as well as about general satisfaction with treatment will also differ. This difference may be even greater between traditional healers and their patients (17).

If we agree with the finding of Frank et al. (25) that the patient who brings positive emotional states and feelings to the therapeutic encounter will experience a reduction in feelings of distress, we would expect greater effectiveness for the patients of spiritist healers than for those of therapists in this study because of the healers' greater positive expectations.

Wilkins (23) suggested that expectancy-related information may affect the outcome of therapy by altering patient selection and changing the frequency of contact as well as the quality of the therapeutic relationship. Spiritist healers seem to have several advantages over community mental health workers. They can select their patients, since many help seekers attend a healing session but only some are called out of the audience to be treated. Spiritists can also be flexible in relation to follow-up visits and the timing and intensity of treatment. Traditional healers are thus more free to schedule their efforts for the greater benefit of patients judged as having good prognoses.

In summary, in this study, the choice of mode of treatment did not significantly depend on type of complaint or level of expectation regarding particular complaints. However, patients who sought spiritist healers seemed more hopeful, which may have contributed to their better prognoses, although this may have been enhanced by healer selection. Those spiritist patients who were dissatisfied with medical doctors or

mental health workers seemed most hopeful, because they viewed the healer as a last resort.

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Medicine Court: *Rogers* in Practice

Jorge Veliz, M.D., and William S. James, M.D.

The authors conducted a prospective study of the impact of the Rogers decision involving patients' right to refuse treatment during the first year (1983–1984) of its implementation in the Massachusetts facility for the criminally insane. They learned that of the 98 cases submitted to the probate court, only 39 were heard. The court found that 35 (90%) of the 39 patients whose cases were heard lacked competence to make treatment decisions. Hearings occurred 2–7 months after petitions were signed by treating physicians. In arriving at the decisions the court appeared to rely more on reports of violent incidents than on evidence of mental illness or testimony about competence.

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During the past decade there has been increasing interest and litigation focused on the issue of the right of mentally ill patients to refuse medication. Courts have viewed antipsychotic medications as having “frequently devastating and often irreversible side-effects” (1) and, therefore, as representing “extraordinary treatment” (1, 2) requiring the informed consent of the patient before administration. First Amendment rights to freedom of religious beliefs (3) and freedom of thought and speech (2), Eighth Amendment protection against cruel and unusual punishment (4–6), and Fourteenth Amendment liberty and due process rights have all been cited as constitutional bases for a right to refuse antipsychotic medication. Nonetheless, the U.S. Supreme Court has not yet recognized any such constitutionally based right.

Medication refusal cases have been heard in Colorado, the District of Columbia, Massachusetts, New Jersey, New York, Ohio, Oklahoma, Utah, and Wisconsin. The resulting decisions provide a wide range of procedures for the use of antipsychotic medications. Some states found no right to refuse medication for committed patients because the commitment process is seen as embodying a finding of lack of competence to

make treatment decisions (7–9). New Jersey established a medically administered review process (10).

The decision that gave the most protection to patients' rights is probably *Rogers v Commissioner of Mental Health* in Massachusetts (2). It states that “commitment to a mental institution is not, in itself, a determination that the patient is not competent to make decisions concerning his treatment” (2). A separate judicial determination of competence to make a treatment decision is necessary. If the patient is found incompetent, then a separate hearing must be held in which a judge, not medical personnel, makes a “substituted judgment decision establishing a treatment plan,” which will then be monitored by the patient's guardian. Psychiatrists must report changes in the treatment plan to the guardian, who may call for a hearing to review the change. In making the substituted judgment, the judge is to consider 1) the ward's expressed wishes regarding medication, 2) the ward's religious beliefs, 3) the effect of the decision on the family, 4) prognosis without treatment, 5) probability of side effects, and 6) prognosis with treatment. Medication may be forced without a previous hearing “only if that patient poses an imminent threat to himself or others and only if no less intrusive method of treatment is available” or if the patient is seen by the doctor as incompetent and “medication is necessary to avoid an immediate, substantial and irreversible deterioration of a serious mental illness” (2).

Although the decision was primarily aimed at resolving problems arising when patients refuse medications, the court added that “because incompetent persons cannot meaningfully consent to medical treatment, a substituted judgment by a judge should be undertaken for the incompetent patient even if the patient accepts the medical treatment” (2). Thus, conceivably, every substantially psychotic hospitalized patient should have competency and substituted judgment hearings. The practical matter of how to implement two adversarial judicial hearings in a timely manner so as not to delay for long periods of time treatment of very sick patients has not been considered to any extent by the court, although there has been mention of a system of “on call” probate judges.

Decisions such as *Rogers* have left psychiatrists concerned about their ability to continue to treat their patients adequately. This is especially true in the public sector, where limitations in funding and the presence of large numbers of very trying patients have long

Received Oct. 11, 1985; revised July 17, 1986; accepted Sept. 4, 1986. From the Department of Psychiatry, Harvard Medical School, Boston; and the McLean/Bridgewater Program, McLean Hospital. Address reprint requests to Dr. Veliz, McLean Hospital, 115 Mill St., Belmont, MA 02178.

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made treatment difficult at best. Psychiatrists have predicted that court-imposed restrictions on their use of antipsychotic medications, the single most effective treatment for psychosis, will lead to a decrease in the quality of treatment rendered, delays in treatment, and enormous expenses in terms of both physician time and dollars (11–14; unpublished 1979 paper of R. I. Shader). Legal advocates have countered that regulations are necessary to ensure due process protection of patients' rights (6, 15, 16). Although there has been much discussion in the literature about these decisions, there are few data about the actual application of procedures mandated by "right to refuse treatment" decisions. In this paper we present data on the first 12 months under *Rogers* in Massachusetts.

SETTING

Bridgewater State Hospital, the Massachusetts strict-security facility for criminally insane men, is operated by the state's Department of Correction; clinical services are provided through a contract with a university-affiliated teaching hospital. The census is generally between 450 and 500 men, most of whom are patients committed for long-term treatment. There are 1,100 to 1,200 admissions per year. About half of the patients are sent from courts for 20- to 40-day pretrial evaluations of competence and criminal responsibility. The rest are transfers from prisons or jails (38%), transfers from the Department of Mental Health's hospitals of men who are too violent to be managed there, commitments for presentencing evaluations, and very small numbers of other court referrals. It is the last stop for men who have been unable to make it in any of the other facilities of the human services system in the state. Schultz (17) noted that following the temporary injunction against the use of involuntary medication at Boston State Hospital in April 1975 (the beginning of *Rogers*), the number of patients transferred to strict security increased significantly (.08/month to .16/month on the Austin Unit; .17/month to .55/month on the May Unit). Some patients were simply refused readmission to Boston State Hospital because it was known that in the past they had refused medication believed necessary. These practices were not limited to Boston State Hospital. We believe that some former patients who could no longer get into hospitals went to Bridgewater through the criminal courts or jails.

Since the majority of Bridgewater patients are actively psychotic, a major function of the hospital is to bring the psychosis under control so that the patient may continue with a court trial or return to the sending institution. Although the highly structured correctional setting of the hospital is often helpful, effective treatment depends on antipsychotic medication. Because more than half of the patients are acutely psychotic on admission, and because a preliminary survey suggested that 60%–70% of the patients were

questionably competent to consent to receiving antipsychotic medication, we conservatively estimated that we might need to do 800 hearings in the first year of operation under *Rogers*. In addition, we identified a much smaller group of patients who had a history of becoming psychotic and then violent when not taking medication and who were refusing medication. Under *Rogers*, it is not possible forcibly to medicate in order to prevent a foreseeable but not imminent emergency unless the patient has been judged incompetent and medication has been authorized by way of a substituted judgment treatment plan. Therefore, we were anxious to proceed with hearings as quickly as possible.

METHOD

The majority of the medical court hearings were observed by one of us (J.V.). To increase internal reliability, several of the hearings were also monitored with the help of a clinicolegal research assistant. The relevant material presented during the medical court hearings was initially independently coded by both observers.

We developed a flow chart that included demographic data on the patients (e.g., diagnosis, treatment plan with antipsychotic medications, refusal or acceptance of medications, incidence of violence, history of mental illness, and admissions to Bridgewater State Hospital). Also charted were length of and steps in court proceedings, testimony of the physician and the guardian ad litem, and court findings. After testimony, we interviewed each physician as to his or her reactions to "medicine court hearings." Results were analyzed by using chi-square tests.

RESULTS

A total of 98 petitions were submitted to the probate court during the first year of *Rogers* implementation, but only 39 cases were heard by the court during this time. Thirty patients for whom petitions were filed were discharged before hearings were scheduled, and 29 cases were carried into the next year. The waiting period between filing the petition and the actual court hearing date was, on the average, 4.5 months (range, 2–7 months).

At the time of the hearings all patients had been involuntarily committed to Bridgewater State Hospital. This meant that the patients had been found by a district court or superior court to be mentally ill, to present a likelihood of serious harm to themselves or others if not hospitalized, and to require strict security. The 98 patients chosen for petitioning were seen as lacking competence to make treatment decisions and were judged most in need of antipsychotic medication of all patients in the hospital. Of the 39 patients whose cases were heard, 22 (56%) were white and 16 (41%)

were black; thus the population was somewhat skewed toward blacks. The most common diagnosis was schizophrenia, paranoid type, chronic. Twenty-four (62%) of the patients had a history of more than one admission to Bridgewater. This rate is consistent with that among the general population of the institution.

A total of 12 psychiatrists, 10 of whom had no previous court experience, were involved in the hearings. The average total number of hours psychiatrists spent on a medical court case was 10.2 per patient (5.1 hours in evaluation review of records and preparation of the medical affidavit and 5.1 hours for time with lawyer, court, and follow-up). The actual total psychiatrist time involved in the 39 hearings was 411 hours—more than 10 weeks of a full-time psychiatrist's time.

In all cases, psychiatrists testified that patients lacked competence to make a treatment decision. In general, they based their conclusions on four kinds of statements: 1) because of the patient's mental illness, he is not rational and therefore not competent, 2) when he does not take medication the patient becomes psychotic and violent, 3) the patient does not acknowledge or understand his illness (he lacks insight), and 4) the patient does not understand the benefits of medication. Because there are no clearly established legal criteria for determining the competence of a patient to decide whether to take antipsychotic medication and because the court did not state any clear criteria by which it was making the competence decision, in practice it appeared to us that the court adopted the standards presented by psychiatrists in their testimony.

In general, psychiatrists, especially those without previous court experience, saw the medicine court hearings as a "new and painful" experience. As one psychiatrist stated, "I wanted to express more but in the adversary system I couldn't. I want to help my patients; that is my role."

The large amount of physician time required per hearing limited the number of cases that could be handled. This, in conjunction with the long delays between the signing of the petition and the hearing, made holding the 800 hearings we had originally estimated for the first year impossible.

Each case required the intervention of at least three lawyers: one defense lawyer, one hospital lawyer, and one guardian ad litem (appointed by the court). The defense attorneys (also appointed by the court) actively represented their clients and in some instances took a strong adversarial role. One defense attorney in cross-examination stated, "Doctor, you're giving medications not because of one person's mental illness but to control their behavior so you can walk safely among them." He also accused the physician of experimenting on the patient with drugs despite the fact that only the usual antipsychotic medications were being given in usual doses. Guardians ad litem in general spent much time reviewing records, interviewing patients, and preparing written reports for the court.

Three judges from the probate court presided over

the 39 medical court hearings. All sessions were heard at the Bridgewater State Hospital. Each judge held four sessions. The average length of a case hearing was 1 hour and 20 minutes. There was no significant variation in the length of case hearings between judges.

Substituted Judgment/Guardianship

For all patients found not competent to make a treatment decision a guardian was appointed, and the substituted judgment made by the judge was that if the patient were competent, he would choose to accept antipsychotic medication for his mental illness. In considering the substituted judgment question, issues of the patient's religion or the family's preference arose in only four cases. Two of these patients were found competent to make treatment decisions; therefore, these issues could have had an impact in only two cases. In these cases a family member was appointed guardian.

In all but six of the cases where the patient was found incompetent the guardian was initially appointed as a temporary guardian for a period of 3 months, after which it was necessary to have a second hearing (which in most cases was similar to the first) to appoint a permanent guardian. Two hearings were necessary in 29 cases. On the average, about 8 months elapsed before a permanent guardian was appointed. In most cases the guardian was a court-appointed "master," although in three cases a family member was appointed.

It is the role of the guardian to monitor the court-ordered treatment plan; thus, psychiatrists are required to report any medication changes to the guardian. The guardian has the right to contest any of these medication changes at a further judicial hearing. This process allowed in one case for a hearing in which the court was asked to decide whether it would order the hospital psychiatrist to give a medication that the patient's attorney felt would be helpful but the hospital psychiatrist did not think would be helpful.

Factors Correlated With Findings of Competence and Incompetence

The relation of the various factors studied to findings of competence and incompetence is summarized in table 1. Of the 39 cases heard, the court found that in 35 (90%), patients lacked competence to make a treatment decision; in four (10%), the patients were found competent. All four of these patients stopped taking medication the day of the hearing. One of the competent patients was discharged, and petitions were repeated for two patients due to substantial clinical deterioration. One of these two patients became markedly psychotic and paranoid about 2 months after stopping medication, and the other assaulted a psychiatrist the day after the hearing. The fourth patient did not deteriorate to the point where repetition was necessary.

TABLE 1. Court Findings in 39 Cases Heard to Determine Competence to Refuse Medication

Item	Patients Found Competent		Patients Found Not Competent	
	N	%	N	%
Race				
White (N=22)	2	9	20	91
Black (N=16)	2	13	14	88
Hispanic (N=1)	0	0	1	100
Diagnosis				
Schizophrenic disorder (N=30)	3	10	27	90
Schizoaffective disorder (N=5)	1	20	4	80
Affective disorder (N=2)	0	0	2	100
Mental retardation (N=2)	0	0	2	100
Admissions to Bridgewater State Hospital				
First (N=15)	1	7	14	93
Second-fourteenth (N=24)	3	13	21	88
Drug side effects				
Present (N=16)	1	6	15	94
Absent (N=23)	3	13	20	87
Medication refused				
Yes (N=22)	2	9	20	91
No (N=17)	2	12	15	88
Incidents of violence reported				
Yes (N=34)	1	3	33	97
No (N=5)	3	60	2	40
Physician had court experience				
Yes (N=3)	0	0	3	100
No (N=36)	4	12	32	89
Recommendation of guardian ad litem ^a				
Patient be found competent (N=5)	3	60	2	40
Patient be found not competent (N=33)	1	3	32	97
Judge				
A (N=16)	3	19	13	81
B (N=11)	0	0	11	100
C (N=12)	1	8	11	92

^aOne of the guardians did not make a recommendation.

The large percentage of patients found not competent, in agreement with the psychiatrist's recommendation, is not surprising because the patients chosen for petitioning to the court were those viewed by the staff as the most disturbed in the hospital.

Race, diagnosis, and number of previous admissions to the hospital did not correlate with court findings, nor did whether the patients were already refusing to take medications.

In all but one case, antipsychotic medication doses fell within the ranges recommended by the APA Task Force on Psychopharmacological Criteria Development (18). During the hearings, the 16 patients who complained of having drug side effects noted dry mouth, blurred vision, constipation, and trembling hands. Five of these patients claimed "unusual" side effects such as "My mind is destroyed," "I have holes in my brain," and "Medication makes me violent." Presence or absence of side effects made no difference in outcome. All but one of the patients with reported incidences of violence were found not competent. Of the five patients without such reported incidents, two were found not competent and three competent. These apparent differences did not reach statistical significance because the number of patients judged competent was too small.

The recommendation of the guardian ad litem

seemed to be well followed by the court (table 1). Again due to the small number of patients found competent, the apparent differences did not reach statistical significance. The numbers involved are also too small to say anything significant about correlations with the physician's previous experience in court or about the judge hearing the case, although there were apparent differences.

DISCUSSION

The data presented here make it clear that in application the Rogers procedures for the administration of antipsychotic medication are extremely time-consuming and cumbersome. They require an enormous investment in professional time (many hours of work for at least three lawyers, a psychiatrist, and a court) for each case.

In addition, it was the subjective impression of several of the psychiatrists involved in the hearings that the process of the hearing adversely affected the relationship between the patient and the treating psychiatrist. We have no clear data on this matter yet, but it is to be noted that one patient assaulted his psychiatrist the day after the hearing and another, who had had a good working relationship with his psychiatrist,

began to express increasing doubt and confusion about whom to trust.

The majority of the 800 anticipated hearings would have involved patients who were accepting medication but who presented a question as to their competence to make treatment decisions. Since these patients had not been adjudicated incompetent, and since it was simply physically impossible to file 800 petitions, most of these patients were medicated. However, after a petition had been filed on a patient, there no longer was a presumption of competence.

During the delay of up to 7 months between the time a physician files a petition and the time the case is heard, there is no legal authority for a physician to medicate a patient who may be incompetent to consent to treatment with antipsychotic medication, regardless of whether the patient agrees to take the medication. The probate court explained this legal predicament by saying, "All of us are new to this procedure."

Implementation of any change in the usual course of practice is always confusing and inefficient. Introducing new laws into systems as complicated as mental hospitals often produces periods of stress and the possibility of adverse effects on treatment. Nonetheless, there is no doubt that protecting a patient's right to be involved in treatment decisions is an important goal, one that is worth some inconvenience.

Data presented here, however, raise questions as to just what it is that has been achieved by the *Rogers* procedures. As noted, the differences found did not reach statistical significance, mainly owing to the very small number of patients found competent. Nonetheless, some trends are evident.

Of the factors reviewed, only the presence or absence of reports of violent incidents and the recommendation of the guardian ad litem seemed to relate to whether the patient was subsequently found competent to make a treatment decision. Both of these factors seemed to relate more strongly to outcome than did the physician's testimony regarding lack of competence due to mental illness. In fact, this is in line with our subjective impression that judges were more interested in testimony about the extent of violence displayed by the patient than they were in testimony about lack of competence to make treatment decisions.

Whether a patient is or has been violent is not an issue that the Massachusetts Supreme Court saw as important in making either the competence or the substituted judgment findings in their description of the *Rogers* procedure. The issue of violence is important in commitment hearings, in which the hospital must demonstrate that, due to his or her mental illness, the patient presents a likelihood of serious harm to self or others and requires strict security. The *Rogers* court, however, was very specific in stating that the fact that a patient has been committed to an institution has no bearing on his or her competence to make treatment decisions. That reports of violent incidents and guardian ad litem recommendations (a lay person's view of a patient's degree of violence and disor-

ganization) are the factors most clearly correlated with the competency decision suggest that the court, in the absence of a clear definition of competence, used violence as an indicator of lack of competence to make a treatment decision.

In all cases where the patient was found incompetent, the substituted judgment decision was that the patient would take medications if he were competent. In only two cases were issues of family wishes or religious concerns even mentioned.

In discussing both *Rogers* (2) and *Roe* (1), the Massachusetts Supreme Court was consistently concerned with the side effects of antipsychotic medication, to the extent that it termed such treatment "extraordinary." The adverse effect of the medication is one of the factors the judge must consider in making the substituted judgment decision. Nonetheless, in this series, despite substantial testimony about side effects, there was no difference in the court's decision between the group of patients with side effects and those without side effects.

In *Rogers* and other cases, legal steps (due process of law) were thought necessary because patients' rights to bodily privacy and freedom of thought and movement might be breached by the use of antipsychotic medication: "This chemical intrusion into patients' bodies interferes with their mental processes and is therefore, when administered involuntarily, a clear and flagrant infringement of First Amendment rights" (1). "Antipsychotic drugs, which are used to prevent violence to other persons, to prevent suicide, or to preserve security, are being used as chemical restraints" (1). If violence and not competence is a deciding factor in the competence hearings, and if there is no evidence that consideration of the side effects of antipsychotic medications or the effect on the family was as important in making the substituted judgment decision (as the Massachusetts Supreme Judicial Court seemed to intend), then one must question whether these hearings are in fact fulfilling their legal goal.

As clinicians who wish to be able to treat our patients in the way we think most effective, we certainly have no argument with the large percentage of hearings that ended with an order to treat the patient. Nonetheless, if the legal goals that are the reason for this procedure are not being met, then we question whether it is worth the very large investment of professional time, enormous treatment delays, and the possible detrimental effects on the relationship between the physician and the patient to go through these proceedings.

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Protecting Third Parties: A Decade After *Tarasoff*

Mark J. Mills, J.D., M.D., Greer Sullivan, M.D., and Spencer Eth, M.D.

The authors discuss current public policy concerning the treatment of potentially violent psychiatric patients and outline some legal and ethical precedents of the current policy. Therapeutic interventions before and after the Tarasoff decision are compared. The authors make specific recommendations for clinicians, who they believe tend to interpret laws too restrictively. They suggest that courts need to rethink current liability standards so that legal decisions can be more clinically informed. Finally, they believe that legislative interventions which specify that warning the potential victim and notifying the police absolve psychotherapists from liability may lead to reflexive rather than reflective management of violent patients.
(Am J Psychiatry 1987; 144:68-74)

Protective privilege ends where public peril begins.

—Justice Tobriner (1)

On September 17, 1985, California Governor Deukmejian signed into law Assembly Bill 1133, a statute that redefines the scope of the psychotherapist's legal duty to protect third parties, as required by the *Tarasoff* decision (2). The new law provides specific criteria for the *Tarasoff* duty. It mandates that if a psychotherapist has a duty to protect when a patient has made a serious threat of physical violence against an identifiable victim, that duty is discharged by making "reasonable efforts to communicate the threat to the victim or victims and to a law enforcement agen-

cy." Although psychotherapists may welcome the clarification of the sometimes vague *Tarasoff* ruling, the new law's implications for clinical practice are not clear.

In Western culture, the extent of professional confidentiality has been debated since the time of Hippocrates in the fourth century B.C. Practices have ranged from total openness in the Middle Ages to nineteenth century insistence on absolute secrecy (3). In recent years what had been an ethical debate regarding medical standards has increasingly become a legal debate, with the courtroom the arena for determining social policy. Beginning with the California Supreme Court's 1974 *Tarasoff* decision, numerous judicial bodies have considered the limitations of patient-psychotherapist confidentiality when a third party is in danger (see table 1).

TARASOFF

The evolution in public policy begins with the *Tarasoff* case (19, 20). Prosenjit Poddar, a voluntary outpatient, had sought psychiatric treatment at a friend's urging. The friend believed Poddar had become pathologically obsessed with Tatiana Tarasoff, a student he had met at a dance. Poddar had tape-recorded conversations with the young woman and spent hours replaying the tapes in order to ascertain her feeling for him.

Initially, Poddar was evaluated at the University of California, Berkeley, student health service by a psychiatrist. Dr. Gold did not believe Poddar required hospitalization; however, he prescribed a neuroleptic and arranged weekly outpatient psychotherapy with a staff psychologist, Dr. Moore. During therapy Poddar revealed his fantasies of harming, and perhaps even killing, Tarasoff. In addition, Poddar's friend told Moore that Poddar planned to purchase a gun. When Poddar discontinued therapy, Moore and Gold agreed that he should be evaluated for hospitalization and

Received Jan. 14, 1986; revised June 17, 1986; accepted Aug. 6, 1986. From the VA Medical Center, Los Angeles. Address reprint requests to Dr. Mills, Psychiatry Service, VA Medical Center (B116A), 11301 Wilshire Blvd., Los Angeles, CA 90073.

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TABLE 1. Court Decisions Concerning the Limitations of Patient-Psychotherapist Confidentiality and Protection of Third Parties

Decision	Court	Duty	Liability	Victim	Violence Foreseeable
<i>Tarasoff</i> , 1974 (1)	California Supreme	Warn	No	Specified	Yes
<i>Tarasoff II</i> , 1976 (4)	California Supreme	Protect	No	Specified	Yes
<i>Macintosh</i> , 1979 (5)	New Jersey Superior	Protect	No	Specified	Yes
<i>Thompson</i> , 1980 (6)	California Supreme	None	No	Not specified	No
<i>Lipari</i> , 1980 (7)	Federal District	Protect	No	Not specified	Yes
<i>Leedy</i> , 1981 (8)	Federal District	None	No	Not specified	No
<i>Doyle</i> , 1982 (9)	Federal District	None	No	Not specified	No
<i>Hasenei</i> , 1982 (10)	Maryland Appeals	None	No	Not specified	No
<i>Furr</i> , 1983 (11)	Federal District	None	No	Not specified	No
<i>Jablonski</i> , 1983 (12)	Federal Circuit	Protect	Monetary damages	Specified	Yes
<i>Brady</i> , 1983 (13)	Federal District	None	No	Not specified	No
<i>Hedlund</i> , 1983 (14)	California Supreme	Protect	No	Not specified	Yes
<i>Petersen</i> , 1983 (15)	Washington Supreme	Protect	Monetary damages	Not specified	No
<i>Clark</i> , 1984 (16)	New York Appeals	Protect	Monetary damages	Not specified	Yes
<i>Schrempf</i> , 1985 (17)	New York Appeals	None	No	Not specified	Yes
<i>Peck</i> , 1985 (18)	Vermont Supreme	Protect	No	Specified	Yes

requested that the campus police intercede to facilitate that evaluation. The campus police went to Poddar's apartment and questioned him about his plans but then left when he denied any intention of harming Tarasoff. Two months later Poddar stabbed Tarasoff to death. California then prosecuted Poddar for first-degree murder (21). He was convicted of second-degree murder; that conviction was subsequently overturned on grounds of improper jury instruction, and Poddar returned home to India (22). Later, in a civil action the Tarasoff family sued the university, including both the therapists and the campus police, for negligence. That suit came to be known as *Tarasoff* (1).

In 1974 the California Supreme Court determined that if the facts in the *Tarasoff* suit were as alleged by the plaintiff, then Drs. Gold and Moore had had an obligation to warn Tarasoff. The court thus established the legal duty to warn (1). However, the court did not hold the psychotherapists liable for failing to confine Poddar nor the police liable for failing to transfer the patient to the county evaluation center (1).

Surely the greatest irony of the *Tarasoff* case is that the therapists did not fail to recognize and act on the threat of violence; however, they did fail to enlist the appropriate legally prescribed aid. At the time Gold and Moore requested the campus police's help in hospitalizing Poddar, California's civil commitment act, the Lanterman-Petris-Short Act, had been in effect less than 2 months. Neither the therapists nor the campus police apparently understood precisely how the civil commitment process worked. The city police, rather than the campus police, should have been called, and Poddar should have been transported to a county psychiatric facility for evaluation. The *Tarasoff* case actually involved not a failure to recognize and act on potential violence, but a failure to use the appropriate social-legal interventions as therapeutic modalities. The result of this misperception was the legal establishment of the policy on the duty to warn.

After the initial *Tarasoff* decision, APA became concerned that such a ruling would have adverse effects on psychotherapist-patient confidentiality, be-

lieved to be essential for successful therapy (23). Because of the importance of the issues involved and because of APA's persistence, the California Supreme Court used a rarely employed option and agreed to rehear the case. In *Tarasoff II* the court held that the duty was to protect, rather than to warn, the intended victim (4). However, the court was vague about how this newly described duty could be discharged. The *Tarasoff II* decision suggested that this duty might be discharged by warning the victim or by calling the police, but it did not rule out conventional clinical interventions (e.g., hospitalization or civil commitment) that had long been made by psychotherapists dealing with potentially violent patients.

ETHICAL PRECEDENTS

The ethical roots of the *Tarasoff* decision are found in the principles of medical confidentiality and beneficence, recognized for two millennia. The Hippocratic oath affirms that "What I may see or hear in the course of the treatment or even outside of the treatment in regard to the life of men . . . I will keep to myself" (24). In the present era, physicians continue to prize the sanctity of the doctor-patient relationship, even as it is encroached upon by the demands of insurance companies, peer review organizations, and other interested third parties (25, 26).

Two arguments have been proposed to justify the enduring importance of confidentiality. Moral deontologists assert that privacy and absolute control over personal information are among the natural rights of man. They argue that since a breach of confidentiality constitutes an assault on human dignity, it is always wrong. The alternative and more widely held justification for the importance ascribed to confidentiality is based on a utilitarian calculation of effects (an assessment of likely outcomes). This position holds that the consequences of violating confidentiality outweigh the possible benefits. Some psychiatrists claim that confidentiality is essential to psychiatric treatment

(27). They believe that without the assurance of complete secrecy, patients would be less inclined to enter treatment and those already in therapy would be unwilling to disclose charged material. Therefore, violating confidentiality would seriously affect the care of the mentally ill, to the detriment of patients and society alike.

Another historic tradition in medicine emphasizes the physician's ethical obligation to act beneficently. This responsibility for altruistic service applies not only to patients but to the community as well. Specific public health interventions, such as quarantining contagious patients, have been common in medical practice for hundreds of years. In direct response to the publication of a series of professional articles on the battered child syndrome, every state in the union has adopted laws requiring physicians to report cases of child abuse (28). In addition, some states have recently passed laws requiring the reporting of abuse of the elderly (29). Interestingly, several years before *Tarasoff* one jurist commented on what he perceived to be his duty to society: "No patient has the moral right to convince his psychiatrist that he is going to commit a crime and then expect him to do nothing because of the principle of confidentiality" (30).

We believe that the responsibility to protect patient confidentiality and to protect community welfare forms the foundation of medical ethics. We do not question the fundamental importance of either duty, despite the inherent potential for conflict. Rather, we recognize that, in accord with the current *Principles of Medical Ethics*, neither duty is absolute: "Psychiatrists at times may find it necessary, in order to protect the patient or the community from imminent danger, to reveal confidential information disclosed by the patient" (31). When examining issues raised by *Tarasoff*, one in effect considers the limits of the duty to protect, not the legitimacy of that duty.

For its part, the legal system has granted privileged-communication status in court proceedings to certain special relationships such as husband-wife, cleric-penitent, attorney-client, and, to a limited extent, psychotherapist-patient. Privileged status is cautiously granted and is based on an understanding that the integrity of the valued relationship requires respect for the inviolability of interpersonal trust (32). Whether, in fact, strict confidentiality is necessary for psychotherapy has become increasingly controversial.

In 1976 Dr. Alan Stone warned that the imposition of a duty to protect would "destroy the patient's expectation of confidentiality, thereby thwarting effective treatment and ultimately reducing public safety" (3). The available data suggest otherwise. A group of psychoanalysts was surveyed 2 months after the notorious break-in at the office of Daniel Ellsberg's therapist. Although this group had over 5,000 patients in analysis at that time, fewer than 15% of them had referred to that highly publicized incident (33). In a separate study of psychiatric inpatients, only 17% said they would leave treatment or stop talking with the

staff if confidential information were revealed without their permission (34). In a more recent report Stone reconsidered his position and concluded that "the duty to warn is not as unmitigated a disaster for the enterprise of psychotherapy as it once seemed to critics like myself" (35). The utilitarian balance seems, then, to shift in favor of confidentiality generally but to permit selected violations when they are justified by the conflicting duty to prevent harm. "It is, indeed, difficult to formulate a moral argument against the position that therapists should act to protect those whom they believe to be endangered, as should all human beings" (36).

We maintain that both medical ethics and legal jurisprudence prefer that confidentiality be preserved whenever possible. Furthermore, there is abundant evidence that in instances where the welfare of society or third parties is seriously threatened, confidentiality should, and indeed must, be breached.

POST-TARASOFF POLICY

Within a relatively short time a series of cases followed *Tarasoff* both within and outside of California (table 1). Perhaps the cases that most concerned psychotherapists were the 1980 *Lipari* decision (7) and the 1983 *Petersen* decision (15). In the first instance an outpatient, evidently disgruntled with his care, threatened to harm others but did not specify whom he would attack or when. The therapist apparently made no intervention, and the patient then purchased a shotgun and fired it in a nightclub, injuring and killing several people. The subsequent court decision extended the duty to protect to apply even in cases where a victim had not been and could not be specifically identified. However, it is important to note that the court, as with *Tarasoff* itself, was dealing with the issue in demur. In such cases, the court assumes the facts as presented by the plaintiff's brief. The court thus addresses a theoretical issue: Was there a duty if the facts were as the plaintiff alleges? Virtually always the defendant's version of the facts is quite different. The *Lipari* case, like *Tarasoff*, did not impose liability; in fact, both cases were settled out of court.

The *Petersen* case extends the *Tarasoff* decision the furthest to date. In this case the female plaintiff was awarded monetary damages for injuries incurred as a result of an automobile accident with a patient who had been released from a state mental hospital 5 days previously. The plaintiff claimed that the patient should not have been released and that the psychiatrist should have reported the patient's parole violation. (It was alleged that the psychiatrist knew that the patient had been convicted of murder and rape.) At the time of discharge, the treating psychiatrist had perceived the patient as fully recovered from a drug-induced (phencyclidine) psychosis. Liability was imposed although at the time of discharge the victim was unknown, the violence was unforeseeable, and the patient had not

directly threatened anyone. Perhaps the court could find no other legal mechanism to compensate the plaintiff. However, in a situation in which the patient was threatening to no one in particular, the decision appears to demand predictive powers that are completely beyond present-day psychiatry.

In a previous paper, Mills reviewed many of the post-*Tarasoff* court decisions concerning the protection of third parties from potentially violent psychiatric patients (37). Using a normative analysis, Mills concluded that these cases largely turn on the issue of foreseeability. When the courts have imposed liability, the identity of the subsequently injured party was known to the psychotherapist (*Macintosh*) (5) or the victim would reasonably have been expected to be in close proximity to the target of violence, as in the case of a young child (*Hedlund*) (14) or a home in the vicinity of a building burned by arson (*Peck*) (18, 38). In addition, threats were specific, the patient's history was overwhelming, and there were breaches of conventional practice, such as failure to obtain the patient's prior medical record (*Jablonski*) (12), (*Peck*) (18, 38), or to examine carefully the patient and his or her medical record (*Clark*) (16). When liability has not been imposed, the patient has, at the time of evaluation, been perceived as not being a threat to any individual or group (*Thompson*) (6), (*Leedy*) (8), (*Doyle*) (9), (*Brady*) (13), (*Furr*) (11), even when the patient had a history of violent behavior or alcoholism (*Hasenei*) (10).

Although the use of a normative approach may seem to suggest that courts are concerned primarily with the overall policy, this is not a fully accurate portrayal of judicial decision making. Public policy evolves only as the courts, attempting to achieve justice in each case, make individual decisions. In the majority of states, no cases involving the issue of third-party protection have been brought to the bar. A few states—for example, Pennsylvania and Maryland—have even considered the issue and have decided against following the policy established in *Tarasoff* (39, 40). Nevertheless, the evident trend continues toward a policy of a duty to warn for psychotherapists. In states where the issue has not been litigated, the conservative assumption is that the court will find a *Tarasoff*-like duty when the issue arises.

In August 1985, the California legislature adopted the first state statute concerning the psychotherapist's duty to warn and protect third parties. The law states more clearly the circumstances in which the duty is applicable. A psychotherapist is liable only "where the patient has communicated to the psychotherapist a serious threat of physical violence against a reasonably identifiable victim or victims." The statute further directs that the duty to warn and protect shall be discharged by "reasonable efforts to communicate the threat to the victim or victims and to a law enforcement agency" (2).

After a decade of litigation, the public policy, as it stands to date, dictates that the psychotherapist is

required to use reasonable care to protect a third party from a potentially dangerous patient. The psychotherapist should use reasonable care in assessing the patient's potential for violence, identifying and notifying the possible victim or victims, and informing a law enforcement agency, sometimes even when no specific victim can be identified.

PSYCHOTHERAPISTS AND TARASOFF

Conscientious psychotherapists have always attended to the potential for violence in their patients. Clinically based decisions and interventions have been employed to treat potentially violent patients. Psychiatrists might increase neuroleptic doses in psychotic patients with violent fantasies or "contract" with patients not to harm themselves or others. Frequently, therapists have hospitalized patients who they believed posed a probable and immediate threat to themselves or others. In the past, psychotherapists also generally had the option to keep a patient hospitalized until, in the therapist's estimation, the potential for violence had been significantly reduced. Both circumstances and the climate of medical practice have changed since that time, however. Commitability has become more an application of legal, rather than clinical, criteria. Involuntary hospitalization in most states is now mediated by court representatives, with the courts bearing the responsibility for decision making. Further, as respect for and trust of physicians in our society have declined, malpractice litigation has dramatically increased, creating an adversarial overtone in the traditional doctor-patient relationship. And finally, legal decisions and statutes previously outlined have formalized the psychotherapist's obligation to make appropriate interventions in protecting third parties from violent patients.

Most psychotherapists are aware of the evolution of external constraints on clinical practice. According to a recent survey by Givelber et al. (41), roughly 90% of psychiatrists had heard of the *Tarasoff* case; surprisingly, nearly all believed the sole method of discharging their legal duty was to warn the potential victim. This is not the case. *Tarasoff II* mandates a duty to protect, not specifically to warn. Protecting includes conventional clinical interventions such as reassessment, medication changes, or hospitalization designed to relieve the patient's symptoms.

The process of intervening clinically with potentially violent patients has been recently discussed (36, 42). Therapists should carefully document their concerns about potential patient violence and their reasoning for whatever clinical intervention they employ. If the therapist feels the need, he or she should seek consultation with a colleague, a forensic expert, or an attorney. Patients can be hospitalized voluntarily or, if necessary, involuntarily. In some circumstances, when the potential victim is an unidentified individual or group (as in the *Lipari* case), the only responsible

intervention may be clinical—for example, hospitalization. In fact, in the *Schremppf* case the psychotherapist was faulted specifically for failing to act clinically, although this decision was overturned on appeal (17).

Monahan has emphasized that in study after study violent behavior has been shown to have no clinically reliable predictive paradigms (43). Several explanations have been proposed for the low correlation between prediction of violence and subsequent violent behavior. These include difficulties in operationally defining dangerousness, low base rates of violent acts, use of inconsistent or incorrect decision rules by therapists, differences between clinical and nonclinical environments, and, most importantly, the passage of relatively long periods of time between assessment and follow-up (44). It would probably be more productive to focus on imminent violence instead of future violence. Clinical assessments of immediate risk, such as those involved in decisions to hospitalize, may be considerably more reliable. For instance, scores on the Brief Psychiatric Rating Scale have been shown to be a significant indicator of violent behavior on a psychiatric ward shortly after admission (45). However, prediction of future violence remains highly problematic, and opportunities for prevention are limited (46).

We suggest that when possible, the clinician shift to the courts the burden of the decision making regarding release from the hospital and long-term treatment of potentially violent patients: This requires that psychotherapists know and make judicious use of the various civil commitment statutes in their state. Specifically, when a psychiatrist is genuinely concerned about a patient's propensity for immediate violence, he or she should initiate civil commitment of the patient at once. Soon thereafter, in virtually every state, the matter of the patient's civil commitment is heard by the court. Because issues of predicting violence are much more public policy than psychiatry, the court is the proper forum for such a decision. Finally, when the psychotherapist does not believe that third-party safety can be reasonably ensured by clinical interventions, he or she will need to warn the third party and, at the same time, notify the relevant local law enforcement agency. Beck (47) and Wulsin et al. (48) have reported instances in which warning has furthered the therapeutic alliance and has contributed to the patient's progress in therapy. One cannot assume, therefore, that warning a third party is inevitably countertherapeutic. Sometimes the duty to warn can be viewed as another available therapeutic option apart from its being a legal requirement.

THE COURTS AND TARASOFF

From a legal standpoint the *Tarasoff* case raises an intriguing and important question: On what standard should civil liability be based? Or, to place the question in a clinical frame, what exactly does "using reasonable clinical care" mean?

Ordinarily, in medical malpractice suits the standard is what a professional with comparable training and experience in the same community would have done when faced with a similar situation. When technologies are precise or when there is a conventional therapeutic practice, this is a sensible standard. Consider the hypothetical case in which an agitated schizophrenic patient is hospitalized by a clinician and treated with antidepressants alone. Suppose, then, that the patient's condition worsens and he or she assaults another patient. Since the generally acknowledged treatment for an agitated schizophrenic patient would be a course of neuroleptic therapy rather than antidepressants, it is apparent that the clinician deviated from the community standard mode of treatment. Legal analysis would generally suggest that in such a case the clinician might well be liable.

In contrast, prediction and assessment of violent behavior do not yet have reliable, clinically validated paradigms (49). At the present time, it is unrealistic to think that psychotherapists can accurately predict violence or would respond in any conventional fashion when confronting a potentially violent patient. As long as our predictive abilities remain immature in this area, the standard of a reasonable degree of skill and knowledge is too rigid. While virtually all professionals might agree that "ordinary care" for an acute schizophrenic patient should include a course of neuroleptics, how can we define ordinary care if there exist virtually no reliable assessment or standard management criteria, as is often the case with the violent patient?

We propose a more flexible liability standard: the substantial departure rule (37). This standard would base liability on criteria that are more clinically informed and relevant to the particular circumstances at hand. To illustrate this standard, suppose that Mr. A presents to a hospital emergency room seeking psychiatric help. Dr. B interviews Mr. A, who explains that his welfare money has run out and that he has increased his alcohol intake. He admits to recent purse snatchings and knifings and is feeling "overwhelmed" but not suicidal or homicidal. Dr. B does not find Mr. A to be psychotic and knows that most patients, even those with a significant history of assaultive behavior, are only rarely violent. While sympathetic to Mr. A's plight, Dr. B decides against admission and instead refers him to an outpatient program. Within 1 hour Mr. A attempts yet another purse snatching and, when the victim resists, stabs and kills her. Suppose it was later discovered that Dr. B had failed to obtain the patient's medical record, which documented a history of frequent knife assaults when he was intoxicated, with several such episodes having occurred after the patient was denied hospital admission. By current community standards of liability, we believe the court might well hold the physician and the hospital liable.

If we use the substantial-departure criteria, the issue would be considered from a slightly different perspective: Were there sufficient reasons to believe that,

although his decision making may not have been ideal, Dr. B departed substantially from conventional practice given that particular clinical setting and circumstance? The question raised in this instance is whether Dr. B was acting in a cavalier or irresponsible fashion or whether he chose a course that many, although not all, reasonable practitioners in similar clinical circumstances would have chosen. We believe that substantial departure criteria would give the courts more leeway in taking into account the real-life dilemmas of clinical decision making. If this were the case, courts would presume that psychotherapists would first apply clinical remedies such as reassessment, changes in treatment, consultation, hospitalization, or civil commitment, rather than relying more heavily on reflexive action such as warning the victim or calling the police. Further, legal action that fails to fully appreciate clinically based decision making will result in less willingness to work with potentially violent and disturbed patients—those who are often in greatest need of help.

LAWMAKERS AND TARASOFF

The 1985 California law, outlined earlier, codifies some aspects of the past decade's judicial decisions. By specifying instances when a patient's threat is serious and delivered toward a reasonably identifiable victim, it takes a first step toward clarifying the circumstances in which the duty to warn and protect exists. The advantage of this code lies in its establishment of explicit standards.

The need for explicit standards has long been felt by psychotherapists. For two legislative sessions California psychiatrists have urged the adoption of such a law. Sponsored originally by the California Psychiatric Association, Assembly Bill 2900 was introduced in February 1984 by Assemblyman Alister McAlister (50). It provided that when a duty to protect exists, it is satisfied by the psychotherapist's making a reasonable effort to communicate the threat of violence to the victim or victims.

The initial bill was opposed by the Citizen's Commission on Human Rights, which claimed the bill removed much-needed protection from the public. Since psychotherapists hold themselves to be experts, it argued, they "should be responsible when their actions or inactions result in injury to another." Fearing an increase in the possibility of danger to the public, Governor Deukmejian vetoed the bill (51).

Assembly Bill 1133, introduced in February 1985, added the new requirement that when a serious threat of physical violence had been made, in addition to warning the victim or victims reasonable efforts should be made to communicate the threat to a law enforcement agency. With this new provision the law was adopted.

Although the new law limits psychotherapists' liability in some cases, it encourages clinicians to respond

to a circumstance in a rote way. No mention is made of protecting a third party through clinical interventions. Further, the statute encourages "defensive medicine." Breaching confidences by warning routinely is analogous to ordering laboratory tests that are not indicated clinically, for fear of liability. Rather than being placed in a defensive position, therapists should be encouraged to approach a situation of potential violence thoughtfully, to use clinical interventions whenever possible to contain the potential violence, and to warn when public policy so counsels (52).

CONCLUSIONS

Law and medicine generally employ different decision-making strategies. As a result, attorneys and psychiatrists often reach somewhat different conclusions (53). Although both agree that society deserves protection from violence and that breaching psychotherapist-patient confidentiality is sometimes necessary, there is little consensus about the most effective manner in which to protect third parties.

Before the *Tarasoff* case, psychotherapists primarily used clinical interventions to deal with potentially violent patients. Although, according to the new California law, psychotherapists can protect themselves from liability by warning the police and third parties, that is not necessarily the best way to protect third parties or to help patients. This is not to say that warning cannot be useful. Warning third parties has been shown to be a therapeutic option that can contribute to the patient's progress in therapy (47, 48). However, warning alone does not always protect third parties (12). Clearly, use of both warning and clinical remedies such as reassessment, consultation, changes in medication, or civil commitment offers more protection for third parties as well as help for potentially violent patients.

To this end, the courts need to become more aware of the merits of clinical intervention and to understand the difficulties that psychotherapists face in predicting violence. Because the prediction of violent behavior does not yet have reliable, clinically validated paradigms (43), the courts should consider using a more flexible liability standard such as the substantial departure rule (37). This action would encourage psychotherapists to work with potentially violent patients and thereby further limit violence caused by the mentally ill. As an important aside, it is noteworthy that the evidence continues to suggest that the mentally ill are no more violent than other members of society and that even if their contribution to societal violence were "treated" away, most societal violence would continue.

As a result of the *Tarasoff* case, its legal progeny, and the new California law, psychotherapists are more aware of their responsibility to protect society. We hope that further judicial and legislative actions will both respect the limitations of predictability and en-

courage thoughtful, clinically based solutions to protect third parties and to help the potentially violent patient.

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The Editor's New Year's Greetings

When Proust submitted the initial portion of *Remembrance of Things Past* to the *Nouvelle Revue Française*, it was summarily rejected by André Gide with the incredulous (and in all likelihood apocryphal) comment, "What kind of novel is this that devotes the first sixty pages to a description of the hero's going to sleep?" Modern editors would live in dread of committing an equally colossal gaffe were they not secure in the knowledge that the wisdom and critical judgment of their reviewers protected them from folly. The *Journal* is no exception; indeed, the Editor is blessed with a cadre of many hundreds of colleagues to whom it is his pleasure to express here his gratitude for their vital contributions as referees of *Journal* manuscripts during the period from November 1, 1985, to October 31, 1986.

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Silvio J. Onesti, M.D.
Mortimer Ostow, M.D.
David G. Ostrow, M.D., Ph.D.
Ekkehard Othmer, M.D., Ph.D.

*Deceased

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Loren Pankratz, Ph.D.
Herbert Pardes, M.D.
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 Jack Zusman, M.D.

The year 1986 has been a busy one for the *Journal*. Not only have the number of submissions substantially increased, but their scientific sophistication and merit have risen to a point where it has become painfully difficult to select those few for which our limited space permits publication. The Deputy Editor, Dr. Morris A. Lipton; the Book Forum Editor, Dr. Nancy C. Andreasen; the Research Consultants, Dr. John J. Bartko and Dr. Lee Gurel; and

the 13 Associate Editors have all given unstintingly of their time and advice and deserve the lion's share of credit for whatever degree of excellence the *Journal* has achieved.

The Editor would be totally grounded without his Editorial Staff; they are his wings, his motor, and his rudder. The Managing Editor, Mrs. Evelyn S. Myers, has been invaluable as copilot and, together with Ms. Linda Loy, the Assistant Managing Editor, and the entire editorial flight crew, has kept us on course and on schedule.

The *Journal*, of course, owes its existence and its raison d'être to its parent Association, and the Editor must express his deep appreciation for the friendship and guidance of our Medical Director, Dr. Melvin Sabshin, and for the unflagging support of the Board of Trustees.

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And so, as we wait poised at the end of runway 1987 for takeoff on the next leg of our flight, the Editor and all his Staff wish our authors, our readers, and our colleagues a safe and happy journey through the next 12 months.

J.C.N.

Psychotropic Drug Withdrawal and the Dexamethasone Suppression Test

Robert P. Kraus, M.D., Margaret Hux, B.A., and Paul Grof, M.D.

In a prospective study of 25 patients from the time of hospitalization, seven had recently discontinued psychotropic agents (including antidepressants, neuroleptics, and benzodiazepines). All seven had positive dexamethasone suppression test results after 1 week of hospitalization. This phenomenon did not occur in any of the other subjects who had not discontinued such medications. Some of the subjects with postdexamethasone cortisol increases reported drug discontinuation in the drug histories they gave at admission, but in three, drug screening provided the only evidence of prior drug use. Medication withdrawal may be an underappreciated confounding variable in DST studies.

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Controversy regarding the clinical utility of the dexamethasone suppression test (DST) (1) has sparked spirited debate. We have suggested that the effects of taking or withdrawing from medication might influence DST results (2); this possibility might explain the variable findings often reported in DST studies, thus increasing the controversy. Most clinicians and researchers have relied on the list of exclusionary criteria and medications for the DST proposed

by Carroll et al. (1) without realizing that this preliminary list was based on single case reports and case series studies published up to 1980 and not on systematic research (1). More recent reports, however, have offered an expanded list of drugs that may influence the DST. For example, carbamazepine (3) and birth control pills (4) have now been reported to produce postdexamethasone cortisol nonsuppression in some subjects.

We have suggested that withdrawal of medications known to affect neurotransmitters which in turn influence corticotropin-releasing factor (CRF) activity could affect DST results (2). Specifically, abrupt withdrawal of medications with anticholinergic (e.g., tricyclics, monoamine oxidase inhibitors [MAOIs], antiparkinsonians, phenothiazines, butyrophenones), antihistaminic (e.g., phenothiazines, tricyclics), antiserotonergic, GABA-agonist (e.g., benzodiazepines), α -2 agonist (e.g., clonidine), opiate agonist (e.g., narcotics), or β -adrenergic-blocking (e.g., propranolol) activity could produce transiently increased CRF activity and, as a consequence, abnormal DST results (4). A report that antidepressant discontinuation can produce high postdexamethasone cortisol levels (i.e., nonsuppression on the DST) for up to 14 days after withdrawal (5) and a single case report of similar dexamethasone suppression test changes after piperacetazine withdrawal (6) tend to support these suggestions. A recent report (7) suggests that a similar phenomenon may occur after cessation of regular-dose diazepam.

We report here preliminary results from a study of recently hospitalized patients which provide further evidence that recent abrupt withdrawal of benzodiazepines, neuroleptics (other than piperacetazine), and antidepressants may produce marked transient increases in postdexamethasone cortisol levels and conversion of DST results from suppression to nonsuppression.

Received Sept. 3, 1985; revised Feb. 18, 1986; accepted May 6, 1986. From the Department of Psychiatry, McMaster University, Hamilton, and Hamilton Psychiatric Hospital. Address reprint requests to Dr. Kraus, P.O. Box 585, Hamilton Psychiatric Hospital, Hamilton, Ont., Canada L8N 3K7.

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METHOD

We studied 25 patients consecutively admitted to a single ward in a large psychiatric hospital, irrespective of diagnosis. Diagnoses were made by the treating psychiatrists, who used *DSM-III* criteria, at the time of discharge.

The DST was performed at least twice: at admission (days 1 and 2 in the hospital) and exactly 1 week later (days 8 and 9). Patients with abnormal values on either DST were then retested if possible. Each DST consisted of determining baseline serum cortisol levels at 3:30 p.m., administering 1 mg of dexamethasone p.o. at 11:00 p.m., and determining serum cortisol levels at 3:30 p.m. and 11:00 p.m. the next day. Dexamethasone ingestion was observed by a ward nurse. Serum cortisol levels were determined in units of nanomoles per liter by solid phase radioimmunoassay with a Coat-A-Count Tube Kit provided by Diagnostic Products. The inter- and intra-assay coefficients of variation were 4.3% and 5.1% for a value of 80 nmol/liter, and 3.5% and 4.2% for a value of 800 nmol/liter. The lower limit of assay sensitivity was 5 nmol/liter (0.2 µg/dl). Nonsuppression was defined as a cortisol level on either DST of greater than 138 nmol/liter (5 µg/dl).

In addition to detailed drug histories obtained from each patient at admission, objective evidence of drug use at the time of admission was obtained by means of quantitative assays for serum alcohol, lithium, tricyclics, phenobarbital, salicylate, phenytoin, and carbamazepine levels and qualitative urine drug screens for phenothiazines, haloperidol, tricyclics, benzodiazepines, anticholinergics, and narcotics. This extended drug screening was undertaken because we hypothesized that these compounds had the potential to influence CRF activity. We were unable to objectively screen for estrogens, birth control pills, antihistaminics, MAOIs, or β-blockers. It is well recognized that drug-screening provides more reliable information about recent drug intake than drug histories (8). No subject met criteria known to invalidate DST results (1). All subjects were weighed weekly.

Statistical analyses were performed initially by comparing changes in plasma cortisol levels (from the first to the second DST) between the group of patients with evidence (by history or drug screen) of psychotropic drug discontinuation at the time of admission and all the other patients (in whom psychotropic drug doses remained unchanged or were increased) with Student's *t* tests (*df*=21). A multiple regression analysis was then performed, which assessed the contribution of each of four variables (drug change, clinical change, sex, and age) in explaining the variability in change in cortisol level from the first DST to the second.

RESULTS

Of the first 25 patients to complete the protocol, nine had evidence of discontinuation of one or more

compounds with potential CRF-inhibiting activity. Of these nine patients, seven had substantially improved clinically after 1 week in the hospital (the time of the second DST) and continued to improve, but all had marked increases in their cortisol levels from the admission DST to the week 1 DST (mean±SD cortisol increase, 206.43±109.84 nmol/liter or 7.48±3.98 µg/dl). None of these seven patients had lost weight during this period; six changed from normal to non-suppressing cortisol levels. The diagnoses, drug changes, and cortisol values for all seven patients are given in table 1. Three of these seven patients (patients 1, 2, and 5) were given another DST 21 days after admission. None had had any further drug changes, and all had returned to normal suppression. All three were tested again 35 days after admission, and all were still suppressing normally. The remaining two patients among the nine with medication discontinuations (one discontinuing regular-dose amitriptyline, 150 mg h.s., plus lorazepam, 1 mg b.i.d.; the other discontinuing desipramine, 150 h.s., plus haloperidol, 5 mg h.s.) experienced similar increases in postdexamethasone cortisol (from mild to marked nonsuppression). These two patients, both of whom had melancholia, deteriorated clinically in their first week in the hospital, which may have been a more important factor affecting the cortisol increases (1), and they were excluded from statistical analysis.

The remaining 16 patients had no cessations of psychotropic or other medications or any lowering of dose. Several had increases in doses of psychotropic agents that they had been taking before admission. None of these 16 patients had any increase in postdexamethasone cortisol (from the first to the second DST); in fact, the group showed a mean±SD decrease in cortisol of -85.88±115.52 nmol/liter (-3.11±4.19 µg/dl).

The difference in net change in postdexamethasone cortisol levels between these two groups was highly significant (*t*=5.66, *df*=21, *p*<.001, two-tailed). There was no overlap between the two groups with respect to the direction of the change in postdexamethasone cortisol levels from the first to the second DST. Fourteen of the 16 patients had equivalent DST results on both occasions (10 suppressors, four nonsuppressors), and two switched from initial nonsuppression to normal suppression.

Multiple regression analysis revealed that medication change status was the only variable that contributed significantly to the changes in DST results, accounting for 66% of the variance of change in cortisol levels, with discontinuation of psychotropic compounds being highly significantly associated with increasing postdexamethasone cortisol levels: effect of adding medications (associated with decreasing postdexamethasone cortisol levels), *β*=44.0, *p*=.005; effect of discontinuation (associated with increasing postdexamethasone cortisol levels), *β*=309.9, *p*<.001. Increasing cortisol levels were also significantly associated with female sex (*t*=0.05, *p*=.05), but this

TABLE 1. Characteristics of Patients With Abnormal DSTs at Week 1 of Hospitalization

Subject	Age (years)	Sex	DSM-III Diagnosis	Drug Changes and Continuations ^a	Postdexamethasone Cortisol Levels (nmol/liter; µg/dl) ^b		Clinical Change to Day 9
					Day 2	Day 9	
1	64	M	Bipolar disorder, hypomanic; lorazepam toxicity (mild)	Lorazepam, 2 mg t.i.d., stopped; lithium, 1350 mg/day, continued; methotrimeprazine, 25 mg h.s., added	34; 1.2	160; 5.7	Toxicity resolved (no evidence of benzodiazepine withdrawal); hypomania settled
2	45	F	Organic depressive syndrome secondary to metastatic bronchial carcinoma	Trimipramine, 100 mg h.s., stopped; chlorthalidopoxide, 25 mg q.i.d., plus Premarin, 0.9 mg/day, continued	85; 3.0	257; 9.1	Less depressed and anxious
3	37	F	Adjustment disorder with depressed mood	Desipramine (detected in urine; dose unknown) stopped	52; 1.8	246; 8.8	Less depressed
4	39	M	Alcohol intoxication with violence	Blood alcohol, 77 nmol/liter 20 hours after admission; diazepam, 10 mg, 1 dose on day 3	54; 1.9	256; 9.1	Intoxication resolved; no psychiatric disorder evident
5	38	F	Schizotypal personality disorder	Alprazolam, 0.25 mg t.i.d. plus pyridium, 200 mg t.i.d., stopped; tranylcypamine, 30 mg/day, stopped on day 3; nitrazepam, 0.5 mg h.s., plus L-tryptophan, 1500 mg h.s., continued	27; 1.0	471; 16.8	Marked improvement in anxiety and insomnia
6	19	M	Mixed toxic psychosis	Marijuana, LSD, amphetamine stopped; diazepam, 15 mg q.i.d. plus chloral hydrate, 500 mg b.i.d., added	43; 1.5	161; 5.7	Psychosis resolved
7	19	F	Histrionic personality disorder	Haloperidol decanoate, 50 mg i.m. (stopped 14 days before admission), and flupentixol, 6 mg/day, stopped; chlorpromazine, 100 mg (2 doses), and diazepam, 5 mg (1 dose), on days 2–4	157; 5.6	346; 12.4	Resolution of behavioral outburst and anxiety

^aDrugs that were stopped were discontinued at the time of hospital admission unless otherwise noted.

^bHigher of either the 3:30 p.m. or 11 p.m. cortisol level; nonsuppression defined as >138 nmol/liter (5 µg/dl).

difference appeared due to an overrepresentation of women (four out of seven) in the drug discontinuation group.

Six (24%) of the 25 patients demonstrated objective evidence of drug ingestion that was at variance with their drug histories. Three of the six patients in the drug discontinuation group who switched to nonsuppression demonstrated objective evidence of the presence of psychotropic drugs that they claimed not to be taking (patient 1, lorazepam and methotrimeprazine; patient 3, desipramine; patient 7, flupentixol). For the other three patients, who were all in the group that did not discontinue their medications, there was no objective evidence of psychotropic drugs that they claimed to be taking.

None of the 25 patients was known to be receiving corticosteroids, nonsteroidal anti-inflammatory agents, or cyproheptadine before admission (all of these may have produced false-negative results on the first DST) (1). No patient started taking any medication known to produce false-positive tests (1) during the study period.

DISCUSSION

The changes in postdexamethasone cortisol levels observed exclusively in the drug discontinuation group suggest that cessation of psychotropic compounds at or shortly after admission contributed to the cortisol increases and the switches from normal suppression to nonsuppression. In patient 1, the discontinuation of lorazepam seemed to be the only factor related to the development of transient nonsuppression. This patient had been a normal suppressor during previous hypomanic or depressive episodes, dating back 5 years, and reverted to sustained normal suppression 3 weeks after admission. Although the relatively high-dose benzodiazepine therapy before admission may have "falsely normalized" the initial DST result (1) (with the second DST result representing unmasked nonsuppression), this seems unlikely given the serial DST results during the index hospitalization and the past history. Abrupt discontinuation of benzodiazepines (even without signs of a withdrawal syndrome) may be more likely than tapered withdrawal to produce transient nonsup-

pression; we have not observed such cortisol increases in three patients who were monitored with serial DSTs before, during, and after tapered withdrawal from similar chronic doses of lorazepam (unpublished observations). Discontinuation of a benzodiazepine (alprazolam) may also have contributed to the DST changes in patient 5. These observations are in accordance with those of Coryell et al. (7), who reported that diazepam discontinuation (by history) was associated with a greater likelihood of postdexamethasone cortisol nonsuppression in a group of patients with anxiety disorders.

In patients 2 and 3 the discontinuation of tricyclic antidepressants seemed to produce nonsuppression. These observations are similar to those reported by Dilsaver and Greden (5). In patient 4 the resolution of an episode of alcohol intoxication, possibly augmented by the aftereffects of a single 10-mg dose of diazepam, seemed to produce postdexamethasone nonsuppression. This patient had no history of alcoholism and no evidence of physical or liver function abnormalities or alcohol withdrawal after admission. Cessation of chronic alcohol intake is well known to produce transient cortisol nonsuppression (9–12), but we are unaware of serial DST studies of subjects with alcohol intoxication or social alcohol use alone. If alcohol intoxication or social use is shown to produce similar cortisol rises after discontinuation, then researchers, to assure valid results, will need to exclude even limited alcohol intake for several weeks before testing subjects taking part in single or serial DST studies. In patient 7, neuroleptic withdrawal may have contributed to the robust increase in postdexamethasone cortisol. Such a phenomenon is suggested by a recent report (13) of increases in serum basal cortisol and β -endorphin levels after neuroleptic withdrawal. For patient 6, the cessation of multiple-drug abuse may have triggered the rise in postdexamethasone cortisol; contrary to previous findings (1), the introduction of high-dose diazepam for 1 week did not normalize DST results, although chloral hydrate may have exerted counterbalancing effects.

This was a prospective study, but without a controlled design, and these results must be considered preliminary, but they do suggest that deliberate or inadvertent withdrawal of antidepressants, benzodiazepines, or neuroleptics may produce transient marked elevations of postdexamethasone cortisol (i.e., nonsuppression on the DST) in some patients. The period after a single episode of alcohol intoxication may reveal similar effects.

Our finding that rebound activation of postdexamethasone cortisol levels is not seen immediately, is present at 8 days, and normalizes within 21 days of compound discontinuation agrees with the findings of others (5). These compounds may tend, via a variety of neurotransmitter actions, to inhibit CRF activity when taken regularly, but compensatory mechanisms (with a common CRF-enhancing effect) may serve to maintain CRF equilibrium as long as the compound is contin-

ued. Abrupt discontinuation may then unmask this compensatory activation, producing enough of a temporary rebound to overcome the suppressing effects of dexamethasone until reequilibration can occur. These findings, in conjunction with those of other investigators (4–7, 13), suggest a need for more systematic studies of the effects of drug discontinuation on the DST to see how often, and with which drugs, this phenomenon occurs.

At present, researchers rarely control for recently discontinued medications in subjects in DST studies, and drug-free intervals before testing are rarely longer than 7 days. Thus, unappreciated drug discontinuation may be a confounding variable in a variety of DST studies. Of the seven patients who had marked increases in postdexamethasone cortisol levels in our study, three gave no history of taking medications that were determined by objective screening to be present. In these patients, inadvertent (and unappreciated by the attending clinicians) discontinuation of such drugs may have produced the cortisol increases. In view of the unreliability of drug histories and regular medication compliance in some patients (8), researchers should consider adding objective drug screening to studies designed to assess the sensitivity and specificity of the DST or its relation to changes in clinical state.

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Relapse in Recurrent Unipolar Depression

David J. Kupfer, M.D., and Ellen Frank, Ph.D.

Treatment of the acute phase of recurrent depression has become both routine and successful in the last decade, but the rates of relapse and recurrence remain a problem. In this study a combined psychopharmacologic/psychotherapeutic approach to the acute and continuation treatment of unipolar depressed patients was used. For 59 patients who completed the continuation phase of treatment, the relapse rate after 8 weeks of recovery was 8.5%. Since other recent studies of recurrent depression have reported relapse rates of 15%–22%, these results suggest that there are advantages in combined treatment.

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In the past decade interest in the natural history of affective illness has increased considerably. Although depression is the most common psychiatric problem for which people seek treatment or from which people suffer without seeking professional help, investigators have only recently paid attention to recurrent affective disorders. Much of this research activity has centered on preventive pharmacologic maintenance treatment for recurrent affective disorders, particularly the use of lithium carbonate in preventing manic episodes in patients with recurrent bipolar disorder. Until recently, relatively little attention has been paid to the long-term treatment of patients with recurrent unipolar depression (1). Nevertheless, the problems of defining and achieving recovery in recurrent disorders and avoiding relapses in such patients are now of major importance to clinicians, epidemiologists, and biological investigators.

One of the first hurdles in developing this investigative expertise is defining what one means by "recovery" and "relapse." While there is considerable dis-

agreement as to whether relapse represents an exacerbation of the symptoms of an ongoing and incompletely treated episode after a recovery period or represents a new episode, there is agreement that the symptoms which constitute a relapse must follow a period of remission and must meet the criteria for either a major episode of depression or minor depression. Naturalistic studies on this topic (2, 3), uncontrolled for treatment, have been available for 10–20 years. Recent reports from the Collaborative Study on the Psychobiology of Depression (4–6) have added substantially to the data base on relapse in major depression during treatment, especially individuals who have repeated episodes of depression. Data from these collaborative studies have demonstrated that individuals with three or more episodes of depression may, in fact, have a relapse rate as high as 40% within 12 to 15 weeks after recovery, even with treatment. While these data are revealing, there has been an increasing need for data on the rate of relapse in controlled treatment trials. Most studies indicate that during active drug treatment the relapse rate is approximately 22% and that under placebo or no-pill conditions rates of relapse may reach 50% or more (7). Our current investigation of recurrent unipolar depression, in which both pharmacologic and psychotherapeutic interventions are used, offers an opportunity to examine this issue of relapse in recurrent depression during a controlled treatment trial.

METHOD

To enter our study of recurrent depression, patients must meet Research Diagnostic Criteria (RDC) (8) for a major primary affective disorder at the time of initial evaluation (9). In addition, all patients must have had at least one other major depressive episode during the preceding 2½ years and one additional major depressive episode during their lifetime; thus they clearly meet the criteria for recurrent unipolar depression. All previous episodes must have required psychiatric treatment or have resulted in considerable functional impairment. All patients must have had at least a 10-week period of remission between the index episode and the previous episode. Patients who are pregnant, who have major cardiovascular, renal, liver, or endocrine disease, who have epilepsy, glaucoma, organic brain syndrome, or mental retardation, or who have a

Received Dec. 6, 1985; revised March 18 and June 9, 1986; accepted June 27, 1986. From the Department of Psychiatry, University of Pittsburgh School of Medicine. Address reprint requests to Dr. Kupfer, Department of Psychiatry, University of Pittsburgh School of Medicine, Western Psychiatric Institute and Clinic, 3811 O'Hara St., Pittsburgh, PA 15213.

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medical history that would preclude the use of tricyclic antidepressants are excluded from the study. Furthermore, the index episode cannot be secondary (concurrent or subsequent) within 2½ years to any other psychiatric or medical illness. Specifically excluded are patients with the following disorders as defined by the RDC: schizophrenia, schizoaffective disorder, unspecified functional psychosis, alcohol abuse, and drug abuse.

All patients are given physical and neurological examinations and are kept free of psychotropic drugs for at least 14 days before the initial psychiatric, sleep, and neuroendocrine evaluations that precede entry into the study. Patients undergo a comprehensive independent assessment to ascertain whether they meet severity criteria for the investigation, which include a Hamilton Rating Scale for Depression (10) score of 15 or more (single rater, 17-item version) and a score of 7 or more on the Raskin Depression Scale (11). All patients gave informed consent in order to participate in the treatment trial.

After initial evaluation, all patients are placed on the same acute treatment regimen, which consists of pharmacotherapy (imipramine, 150–300 mg/day) and psychotherapy based on the work of Klerman and associates (12). An attempt was made to treat all the patients in the protocol with 200 mg/day of imipramine, and adjustments during the acute treatment phase were carried out to maximize clinical efficacy or reduce adverse effects. The majority of the patients responded to the 200-mg imipramine regimen. Patients have a psychotherapy session weekly for the first 12 weeks, every other week for the next 8 weeks, and then monthly until they have completed a continuation treatment period of 20 weeks, during which their drug dose has not changed and their rating scale scores have remained stable and consistent with a clinical remission (Hamilton scale score ≤ 7 ; Raskin scale score ≤ 5). When patients have been in the study for 6–8 weeks, they and their family members and friends attend an all-day workshop on the causes and treatment of depression and the goals of the study.

This report is based on the first 119 patients to enter the study. The group consisted of 27 men and 92 women with a median age of 39.25 years and a median age at the onset of illness of 24.6 years. The mean \pm SD duration of the index episode at the point of entry into the study was 23.4 ± 16.6 weeks. Although a minimum baseline Hamilton depression score of 15 was required for entry, most patients had a considerably higher rating: the mean \pm SD score on entry was 22.7 ± 4.8 . Three patients had had two previous episodes of major depressive disorder, and the remaining 116 had had three or more previous episodes (median = 4.2 episodes). This determination was based on data obtained from the Schedule for Affective Disorders and Schizophrenia (13), administered to the patients on admission to the study, and from the Lifetime History of Affective Disorder (14), administered during the clinical remission period. In this study relapse was defined

TABLE 1. Clinical Characteristics of 59 Patients With Recurrent Depression Who Completed the Continuation Phase of Treatment

Characteristic	Mean	SD	Median
Age (years)	41.0	10.8	39.8
Age at onset (years)	27.5	9.8	24.7
Number of previous episodes	6.5	7.0	4.2
Duration of index episode (weeks)	23.4	18.2	16.2
Baseline Hamilton scale score	21.7	5.0	20.4

as again meeting the criteria for a major depressive episode after at least 8 weeks of recovery (4).

RESULTS

Of the 119 patients, 80% ($N=95$) remained in the study for the first 4 months. On the basis of our criterion of a Hamilton score of ≤ 7 , 67 of these 95 patients had developed a clinical response within 16 weeks. Seventy-seven of the 119 patients completed the acute treatment phase and entered the continuation phase; 59 of the 77 patients completed the continuation phase, and four patients remained in the continuation phase at the time of this report.

The group of 59 patients who completed the continuation phase consisted of 13 men and 46 women, who had diagnoses of bipolar II disorder ($N=5$), endogenous depression ($N=38$), and psychotic ($N=1$), incapacitating ($N=5$), agitated ($N=5$), and retarded ($N=8$) depression. As shown in table 1, these patients demonstrated no differences in clinical characteristics from the overall group of 119 individuals described in the Method section.

Of the remaining 14 patients who reached the continuation phase but who failed to complete the 20 weeks of continuation, nine suffered a recurrence of symptoms—four patients showed a recurrence of symptoms within 4 weeks of entering the continuation phase (two within 10 days, one within 2 weeks, and one within 4 weeks); five patients suffered a relapse after 8 weeks of recovery. Therefore, if one uses the criterion of 8 weeks of recovery, there were only five patients (8.5% of the 59) who met our criterion for relapse. If one uses the more liberal 2-week definition of relapse, then 15.3% ($N=9$) of this sample of 59 suffered a recurrence of symptoms.

Five patients did not complete the continuation phase and left the study in a state of clinical symptomatic remission: one patient unexpectedly moved out of the state, three patients dropped out of the study because of their noncompliance with the treatment protocol, and one patient had sufficiently adverse side effects to withdraw from the study.

The paucity of relapses (five) necessitates a descriptive rather than a statistical approach. The mean length of time it took for the patients to go into relapse after entering continuation treatment was 21.4 weeks; the median was 16.9 weeks. (This reflects the data of one patient who stabilized at several different occa-

sions during the continuation phase, thus necessitating additional symptom-free periods during continuation therapy.)

DISCUSSION

The current literature on "naturalistic" treatment follow-up suggests that the cumulative rate of relapse after recovery for individuals with primary depression is approximately 15% at 6 months and 22% at 1 year (3, 4). While the patients on whom these rates are based met criteria for primary depression, most of them had had fewer than three episodes. A further refinement in the most recently published analyses of these data indicates that 11% of the patients who had had fewer than three episodes relapsed within 12–15 weeks, but 43% of the patients who had had three or more episodes suffered a relapse by the 12th week. Thus, these patients with recurrent unipolar depression, who were not entered in a controlled drug trial, experienced a 40% relapse rate within 4–5 months after recovery. These data from the Collaborative Study on the Psychobiology of Depression are consistent with the recent review of continuation treatment by Prien and Kupfer (7), which demonstrated that the relapse rate was at least 22% for patients in the active drug condition versus 50% for those in the placebo condition. Since our patients received a dose of imipramine during continuation which was similar to that of the patients in the Prien and Kupfer review, the lower relapse rate in the present study does not appear to be simply a function of drug dosage.

Our data suggest that the addition of psychotherapy, as well as the educational workshop offered in this protocol, to a major clinical protocol may reduce the rate of relapse to below 10%. This finding needs to be replicated; the second half of the sample for this investigation will offer us the opportunity to do so. Furthermore, a randomized trial in which patients receive concurrent psychotherapy and pharmacotherapy or pharmacotherapy alone during the continuation phase of treatment would present the opportunity for the most definitive confirmation of this hypothesis.

Previous studies on recurrent depression point to the high rate of relapse and the relatively low complete recovery rate compared to the rates for nonrecurrent affective disorders. Unfortunately, little is known about the contribution made by relapse rate to the number of suicides and suicide attempts during recovery. Only additional studies using combined treatment

with longitudinal follow-up can answer this question. Finally, there is a lack of studies on relapse rates in patients with bipolar disorders for whom any form of psychotherapy has been conducted. Current pilot work at the University of California, Los Angeles, (personal communication from Dr. Kay Jamison) points to the advantages of combining psychotherapy with lithium carbonate in the long-term treatment of bipolar disorders. In conclusion, this paper suggests the need not only for focusing our attention on acute and maintenance treatment but also for examining very carefully the aspects of treatment that are most successful during the continuation phase.

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Nocturnal Penile Tumescence in Depressed Men

Michael E. Thase, M.D., Charles F. Reynolds III, M.D., Larry M. Glanz, Ph.D.,
J. Richard Jennings, Ph.D., Deborah E. Sewitch, Ph.D.,
David J. Kupfer, M.D., and Ellen Frank, Ph.D.

Nocturnal penile tumescence recordings were performed in 10 men with major depression and 10 age-matched healthy control subjects to evaluate the possibility that clinical disturbances in sexual interest and activity often reported by depressed persons are associated with objective changes in sexual neurophysiology. Depressed men had significantly reduced minutes of tumescence time, a finding that was not attributable to alterations in sleep efficiency or REM sleep time. Three depressed men had baseline tumescence profiles suggestive of "organogenic" impotence, which improved after recovery. The authors discuss the implications of such findings for clinical practice and future research.

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Depressed persons commonly report decreased libido, reduced sexual activity, and diminished ability to achieve orgasm (1). Specifically, depressed men sometimes report changes in erectile function (2-3). It is unclear, however, if such changes are the result of motivational factors (i.e., pervasive anhedonia or loss of interest), reflect primary alterations in sexual neurophysiology, or represent a combination of these factors. The study of objective correlates of sexual neurophysiology in depressed individuals may help to clarify this issue. With respect to possible neurophysiological changes in depressed men, assessments of nocturnal penile tumescence (4-6) might provide objective correlates of altered sexual function. Episodes

of penile tumescence normally occur throughout the night in association with periods of REM sleep in healthy men of all ages (4-6). Moreover, on the basis of extensive clinical studies, it is widely believed that markedly diminished tumescence is reflective of organically caused forms of impotence, whereas psychogenic sexual difficulties appear to be characterized by relatively normal tumescence profiles (4-6).

A report by Roose et al. (3) demonstrated a virtual absence of tumescence time in two severely depressed hospitalized men with histories of sexual impairment during their depressive episodes. Sexual function and tumescence results were found to improve after clinical recovery. For the current report, we hypothesized that 1) diminished tumescence is an episode-related feature of depression in men, 2) tumescence diminution may be similar to profiles seen in men with impotence from organic causes, and 3) such changes, when present, will be reversible on recovery from depression. We tested these hypotheses on 10 depressed men and 10 age-matched normal control subjects.

METHOD

We studied 10 outpatients seeking treatment for depression at the Western Psychiatric Institute and Clinic. They were not preselected on the basis of a history of sexual dysfunction; in fact, patients with a history of sexual difficulties antedating the current depressive episode were excluded. All patients met the criteria of *DSM-III* and the Schedule for Affective Disorders (7)/Research Diagnostic Criteria (8) (SADS/RDC) for major depressive disorder, had 17-item Hamilton Rating Scale for Depression scores ≥ 14 (mean \pm SD = 19.4 ± 4.9), and ranged from 22 to 44 years in age (mean \pm SD = 33.2 ± 7.2 years). The sample was heterogeneous with respect to various subtypes of major depression (two bipolar, eight nonbipolar; eight primary, two secondary; two melancholic, eight nonmelancholic; six probable or definite endogenous, four nonendogenous; eight recurrent, two single episode). Healthy control subjects were recruited for voluntary participation from university staff and their relatives ($N=8$) as well as other sources ($N=2$) and were matched for age (± 5 years) (mean \pm SD = 32.6 ± 5.7 years). No control subject had a Hamilton score above

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3 or showed evidence of psychiatric illness on the basis of evaluation on the SADS—Lifetime Version (SADS-L) (9).

The results of a physical examination and laboratory studies, which included complete blood count, chemistry profile, thyroid function studies, and ECG, were normal for all depressed men and normal control subjects. Potential subjects with a history of cardiovascular diseases, urologic disorders, endocrinopathy, neurological illnesses, or hypertension were excluded from study. All subjects completed a supervised minimum 2-week drug- and alcohol-free observation period before sleep-tumescence studies were begun and provided written informed consent for research participation. Clinical histories of the depressed men indicated that eight were experiencing decreased libido; three reported difficulty maintaining an erection or achieving orgasm during the current episode of depression. None of the control subjects was experiencing sexual dysfunction. All patients and control subjects reported heterosexual orientation.

Nocturnal penile tumescence measurements were recorded in conjunction with all-night EEG sleep studies over two or three consecutive nights. Our methods for monitoring and scoring EEG sleep studies have been described in detail elsewhere (10, 11). Penile circumference changes during episodes of tumescence were monitored nightly by the use of two mercury-filled strain gauges, one placed at the base and one at the tip of the penis. Circumference changes were recorded polygraphically; an episode of tumescence was defined by an increase in base circumference corresponding to a ≥ 3 mm change over a 60-second period, which is consistent with the published criteria of Karacan et al. (4). As also described by Karacan et al. (4), episodes of tumescence characterized by a ≥ 15 mm increase in tip and base circumference were classified as full tumescence, whereas episodes with tip and base changes between 3 and 15 mm were considered partial tumescence. Sleep and tumescence records were scored manually by registered polysomnographic technologists who had no knowledge of clinical diagnosis.

Reliability of manual scoring of tumescence variables was studied in two subjects by comparing the independent ratings of seven polysomnographic technologists with the ratings of one of us (D.E.S.), a certified clinical polysomnographer. Mean percent agreement was satisfactory ($>80\%$) for all tumescence variables except the full/partial dichotomy, which was somewhat lower (67%).

Sleep and tumescence data were analyzed by applying a series of two-tailed *t* tests to the mean values of nights 1 and 2. The alpha rejection level was set at the stricter .01 level because of the high number of planned comparisons. Variables of particular interest included the number of tumescence episodes (partial, full, and total), minutes of tumescence, and percent of tumescence episodes associated with REM sleep. The possibility that alterations of tumescence time might be associated with differences in time spent asleep or

REM sleep time in depressed subjects was controlled by examining the ratios of tumescence to time asleep and to REM time in both groups. A series of split-plot, repeated measures analyses of variance (ANOVAs) were performed on sleep and tumescence data, with night of study (i.e., night 1 or night 2) as the within-subject factor and diagnostic group (i.e., depressed or normal control) as the between-subjects factor. These analyses also allowed for the detection of possible interactions between diagnostic group and night of study.

Pearson product-moment correlation coefficients also were computed to examine the relationship between age and 1) minutes of tumescence, 2) the tumescence to time asleep ratio, and 3) the tumescence to REM time ratio. Prior research (4) had suggested that minutes of tumescence decrease with advancing age, and it is possible that such an age-dependent relationship may be exaggerated in depression (11).

Visual inspection and maximum penile buckling force determinations were performed during a third study night for eight depressed and seven control subjects. The remaining two patients and three control subjects were studied before inclusion of these procedures as a standard part of the sleep-tumescence protocol. Such direct observational techniques are considered important, since tumescence episodes may sometimes be characterized polygraphically as full yet appear flaccid on visual inspection (12, 13). Subjects were briefly awakened at the point of maximal tumescence during each episode of tumescence on night 3. Visual estimates of fullness of erections (0%–100%) were made independently by the subject and the technician. Night 3 evaluations were conducted by either male technologists (6 nights), female technologists (7 nights), or a male-female team (2 nights). There were no significant differences in visual inspection or buckling force determinations as a function of sex of technologist. Interrater reliability of visual estimates was high ($r=.93$, $df=3$, $p<.05$).

Penile buckling force was measured for each episode of tumescence on night 3 by means of a device consisting of a large syringe with a rubber cap at one end and a sphygmomanometer on the other. The capped end was gently pressed against the glans of the penis toward the penile base, and the force being applied at the time the subject's erection first bent (buckled) was recorded as the buckling force. The device was calibrated such that a 500-g force corresponded to a sphygmomanometer reading of 60 mm Hg. Clinical studies have suggested that a buckling force ≥ 500 g normally corresponds to an erection of sufficient rigidity to permit vaginal penetration (I. Karacan, verbal communication, Oct. 4, 1985).

Night 3 visual inspections and buckling force determinations were used as standards for comparison. For example, diminished tumescence time was considered suggestive of organically caused impotence only if associated with visually determined flaccid erections and buckling forces of <500 g.

TABLE 1. Selected EEG Sleep and Tumescence Variables in 10 Depressed Men and 10 Normal Control Subjects on Nights 1 and 2

Variable	Depressed Men		Control Subjects		t
	Mean	SD	Mean	SD	
Sleep efficiency (%)	80.5	10.6	83.1	14.3	0.46
Time asleep (min)	344.9	48.8	359.9	63.7	0.59
REM latency (min)	65.0	21.2	76.9	36.2	0.89
REM time (min)	72.8	13.3	77.5	16.0	0.71
REM activity (min)	87.1	25.8	94.7	35.0	0.55
REM density (U)	1.21	0.25	1.20	0.29	0.03
Delta sleep (%)	10.8	7.9	12.3	6.9	0.47
Tumescence episodes					
Partial	1.25	1.11	2.00	1.84	1.09
Full	2.45	1.62	2.00	1.84	0.57
Total	3.55	0.76	4.00	0.62	1.42
Tumescence time (min)	95.1	28.5	158.6	45.6	3.73 ^a
Tumescence to time asleep ratio	0.27	0.07	0.46	0.16	3.27 ^a
Tumescence to REM time ratio	1.32	0.37	2.21	0.91	2.88 ^a
REM-associated tumescence episodes (%)	90.1	15.0	81.7	14.6	1.27

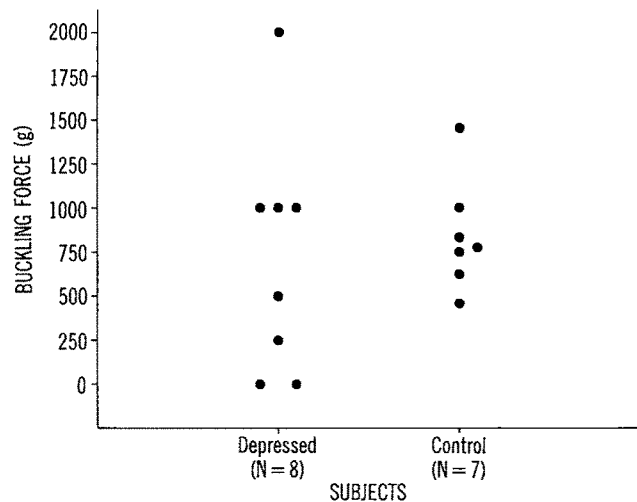
^a $p < .01$.

RESULTS

The mean values of two nights for selected EEG sleep and tumescence variables are summarized in Table 1. The mean values for depressed patients did not significantly differ from those of control subjects on any of the EEG sleep variables that are commonly altered in endogenous depression (i.e., sleep efficiency, REM latency, REM density, and slow-wave sleep time). However, consistent with previous research (10, 11), six depressed patients and only one control subject had REM latency values < 60 minutes (Fisher's exact probability test, $p = .03$). Depressed and control subjects showed a similar number of partial, full, and total tumescence episodes as well as a comparable percentage of tumescence episodes associated with REM sleep. Depressed patients exhibited significantly reduced minutes of tumescence compared with control subjects, who had a mean value nearly 2 SDs higher. Adjustments for time asleep or REM time similarly reflected diminished tumescence time in depression. Repeated measures ANOVAs revealed no significant effects by study night, and there were no significant Group by Night interactions.

Age was not significantly associated with minutes of tumescence ($r = .08$, $df = 18$, $p = .74$), the tumescence to time asleep ratio ($r = .11$, $df = 18$, $p = .64$), or the tumescence to REM time ratio ($r = .08$, $df = 18$, $p = .73$) for the total sample. Age also was not significantly correlated with any of these variables when the depressed and control groups were analyzed separately (all r values $\leq .40$ and p values $\geq .30$).

Buckling force determinations are presented in figure 1. Inspection of individual subject data revealed that three depressed men showed the previously specified

FIGURE 1. Maximum Penile Buckling Force Determinations in Eight Depressed Men and Seven Normal Control Subjects

combination of reduced tumescence time (i.e., a mean value of at least 1 SD lower than the control mean), flaccid erections on visual inspection, and abnormally low buckling force. All three individuals reported reduced sexual interest; two of these men had reported erectile difficulties during their depressive episodes. Follow-up studies were completed on these men after clinical improvement (table 2). Each patient had achieved a stable level of recovery (Hamilton scale scores ≤ 6) for at least 4 weeks before the follow-up studies. Patient 1 had responded to treatment with cognitive therapy and was medication free at follow-up. Patients 2 and 3 did not achieve an acceptable level of symptomatic improvement after cognitive therapy but subsequently responded to antidepressant medication. Follow-up evaluation revealed normalization of buckling force (> 500 g) in all three patients in conjunction with clinical improvements in libido and sexual function. Patients 2 and 3 also showed an increase in the number of episodes of tumescence meeting criteria for full tumescence. However, only the medication-free patient (patient 1) experienced a substantial increase in minutes of tumescence. In fact, patient 3 actually showed a marked drop in minutes of tumescence at follow-up, despite increased buckling force, which may indicate that selected antidepressants such as imipramine suppress tumescence time in addition to REM sleep indexes (11).

DISCUSSION

Nocturnal penile tumescence studies are increasingly used to evaluate disorders of impaired sexual function in men (4–6). Marked diminution of tumescence time, particularly if coupled with flaccid erections and low buckling force, generally is found in men with organogenic impotence (4–6). Although such patients often suffer from documentable and irreversible neu-

TABLE 2. Findings for Three Depressed Men With Abnormal Baseline Sleep-Tumescence Studies Before and After Cognitive Therapy and/or Antidepressant Treatment

Variable	Patient 1		Patient 2		Patient 3	
	Before	After	Before	After	Before	After
Age (years)	27		44		40	
Hamilton depression scale score	17	4	19	6	28	5
Medication	None	None	None	Imipramine, 400 mg/day	None	Imipramine, 200 mg/day
Total tumescence episodes ^a	3	4	3	3	3	2
Full ^a	3	4	2	3	0	2
Partial ^a	0	0	1	0	3	0
Tumescence time (min) ^a	60	104	115	125	87	34
Tumescence to time asleep ratio ^a	0.16	0.28	0.34	0.39	0.24	0.10
Tumescence to REM time ratio ^a	1.28	1.33	1.72	2.50	1.07	0.89
Maximum buckling force(g) ^b	0	500	0	833	250	1000

^aNight 2 of sleep-tumescence studies.^bNight 3 of sleep-tumescence studies.

ropathic or peripheral vascular disorders, whether or not emotional distress also might produce diminished tumescence has long been a controversial issue (3, 5). Overall, our preliminary findings suggest that nocturnal penile tumescence is altered in major depression in terms of decreased minutes of tumescence but not with respect to the timing or amplitude of episodes of tumescence. However, the presence of a subgroup of depressed men with penile tumescence findings suggestive of reversible organically caused impotence also provides some support for the earlier work of Roose et al. (3).

A practical implication of these preliminary observations, if they are replicated in a larger sample, is that depression may produce false-positive nocturnal penile tumescence test results. Impotent men with tumescence findings suggestive of organic impairment should be carefully evaluated for signs of depression and, if indicated, vigorously treated before consideration of a surgical procedure such as the penile implant. However, as illustrated in one of the cases reported here at follow-up, antidepressant medication also may have a deleterious effect on selected aspects of tumescence. Thus, whenever possible, diagnostic nocturnal penile tumescence studies should be completed when patients are medication free.

These results also suggest that decreased sexual interest and activity are associated with objective physiological changes in at least some depressed men. Hence, a simple motivational explanation of sexual impairment in depressed individuals is not supported by our data. In future studies, we plan to explore potential clinical and neurophysiological correlates of diminished nocturnal penile tumescence in depression. Our findings suggest that a clinical history of episode-related sexual difficulties may identify depressed men with diminished tumescence. In our small sample of depressed patients, there were no clear correlations between diminished tumescence and age and between diminished tumescence and severity or subtypes of major depression. Studies of the potential relationships between sleep-related tumescence and neuroendocrine or neurochemical disturbances may also be helpful in

elucidating the mechanisms of diminished tumescence in depression.

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Mania Following Head Trauma

Sashi Shukla, M.D., Brian L. Cook, D.O., M.S., Sukdeb Mukherjee, M.D.,
Charles Godwin, M.D., and Morton G. Miller, M.D.

The authors present psychiatric and neurologic data on 20 patients who developed mania after closed head trauma. An association was seen between severity of head trauma (based on length of posttraumatic amnesia), posttraumatic seizure disorder, and type of bipolar disorder. The manic episodes were characterized by irritable mood rather than euphoria and by assaultiveness. Psychosis occurred in only 15% of the sample, and 70% had no depressive episodes. Bipolar disorders were absent among 85 first-degree relatives. The authors suggest that posttraumatic seizures may be a predisposing factor in posttraumatic mania.

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An association between behavioral disturbances following head injury and brain damage was noted as early as the 16th century, when Fabry observed that head trauma preceded "insanity" in some cases. At the turn of the century, Adolf Meyer described a series of patients who developed "post-traumatic insanity" characterized by neuropsychological and psychiatric deficits. Some authors have noted that patients with periodic psychoses were found during post-mortem examinations to have discrete cerebral lesions. Pilez (1) and others (2, 3) noted an association between periodic mania and brain damage in the 1900s. Von Krafft-Ebing (3) observed that periodic psychosis could be acquired through a head injury. In 1920 Rittershaus (4) reviewed manic-depressive psychosis and concluded that it represented a symptom complex of various organic etiologies. The era of neurosurgery in the 1930s ushered in reports of mania following surgical procedures on the brain. Foerster and Gogel (5) implicated the hypothalamus, while Hoheisel and Walch (6) reported five cases of

manic-depressive illness after such procedures on the midbrain. The latter group distinguished their post-traumatic manic-depressive subjects from more typical bipolar patients by noting fluctuations of mood that were more rapid, lasting only hours or days. Parker (7) first observed the absence of family history in a patient who developed marked mood swings after closed head injury. Achte et al. (8) reported that they had observed mania in three of 47 victims of head trauma.

More recently, Krauthammer and Klerman's concept of secondary mania (9), followed by DSM-III's inclusion criteria for organic affective syndrome, helped establish the etiologic, diagnostic, and treatment significance of mania following cerebral insult. However, Krauthammer and Klerman's review of cases did not include posttraumatic mania, and DSM-III states broadly, "Structural disease of the brain is a rare cause" of organic affective disorders. A recent literature review of posttraumatic mania revealed only a few single case reports (10, 11). Despite these reports, posttraumatic mania is not mentioned in the list of organic manic conditions in Stasiek and Zetin's update (12) of Krauthammer and Klerman's 1978 report. Finally, although severity of brain damage has in general been noted to be associated with psychiatric disability (13), to our knowledge its association with posttraumatic mania has not been reported.

We systematically studied the phenomenological breakdown of symptoms and course of illness in 20 patients with posttraumatic mania. We then correlated the severity of the trauma with the psychiatric and neurologic symptoms in these patients.

METHOD

The study was conducted during a 4-year period ending in March 1984. The subjects were recruited through the neuropsychiatric outpatient clinics of a large municipal hospital in New York City and a suburban university hospital. Patients with primary neurological diagnoses and associated psychiatric symptoms were referred by neurologists, neurosurgeons, consulting psychiatrists, and other treating physicians at the two centers. The study sample consisted of 20 patients, three blacks and 17 whites, and had a male-female ratio of 3:1. Fourteen patients were single, three were married, and three were separated or di-

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TABLE 1. Neurologic Findings in 20 Patients Who Became Manic After Mild, Moderate, or Severe Closed Head Trauma

Severity of Trauma	EEG		Clinical Neurologic Deficit		Cause of Head Injury	
	Finding	N	Finding	N	Finding	N
Mild (N=3)	Normal	3	Postconcussion syndrome	3	Fall	2
Moderate (N=4)	Generalized diffuse dysrhythmia	1	Posttraumatic seizures	1	Moving object hit head	1
	Normal	2	Postconcussion syndrome	3	Motor vehicle accident	2
	Seizure focus	1			Object hit head	2
Severe (N=13)	Seizure focus	3	Right hemiplegia	2	Motor vehicle accident	11
	Generalized diffuse dysrhythmia	1	Left hemiplegia	2	Fall from height	2
	Normal	4	Postconcussion syndrome	3		
			Posttraumatic seizures	9		

vorced. The mean \pm SD age of the sample at the time of evaluation was 33.5 ± 11.0 years, and their mean level of education was 12.7 years.

The patients were administered a structured interview and the Schedule for Affective Disorders and Schizophrenia—Lifetime Version (SADS-L) (14), on which *DSM-III* and Research Diagnostic Criteria (RDC) (15) diagnoses were based. Semistructured interviews were conducted with the available first-degree relatives to establish familial RDC diagnoses. Hospital records were reviewed to corroborate the psychiatric and neurologic histories, and EEG findings were carefully examined.

Only patients who had given verbal informed consent, had clear histories of head trauma, and met the RDC criteria for manic or schizoaffective disorders after the injury were included. To facilitate subdivision of the manic syndromes seen, the RDC were used. This system allowed the diagnoses of bipolar I, bipolar II, and schizoaffective mania following head trauma. In *DSM-III* the criteria for organic affective disorder lack such descriptiveness and schizoaffective disorder is undefined. It should be noted, however, that all our patients met the *DSM-III* criteria for organic affective syndrome. The severity of head trauma was based on the duration of posttraumatic amnesia and classified according to Russell as mild, moderate, or severe (16). Each patient had suffered blunt head trauma resulting from either the impact of a moving object on his or her stationary or slow-moving head (acceleration) or deceleration of the head and body by a stationary or slower-moving object (17). The patients were civilians, and all head injuries were of the closed type.

RESULTS

Of the 20 patients, 13 were classified as having had severe head trauma, four had had moderate trauma, and three had had mild head trauma. Their posttraumatic neurologic deficits are summarized in table 1. The seizure foci on the EEGs indicated temporal or temporoparietal abnormalities in nine patients—on the left side in five patients, on the right in three patients, and on both sides in one. Clinically, 10 of the 11 patients with abnormal EEGs had posttraumatic

seizure disorders; eight had partial seizures and two had primary generalized seizures.

Table 2 contains the ages, psychiatric characteristics, and trauma severities of the individual patients. The mean \pm SD age at the time of head trauma was 24.7 ± 10.4 years, and the age at onset of the psychiatric illness was 27.5 ± 9.0 years. The time between head trauma and onset of psychiatric illness was 2.8 ± 3.4 years.

According to the RDC, after head trauma 13 patients had bipolar I illness, three had bipolar II illness, three had schizoaffective mania or depression, and one patient had hypomania. Comparing the severity of head trauma to the psychiatric diagnosis (table 2) revealed that the 16 patients with bipolar I or schizoaffective illness had had moderate to severe head trauma, the three patients with bipolar II illness all had had mild head trauma, and the patient with chronic hypomania had had severe trauma.

Fourteen (70%) of the patients experienced recurrent mania without depression, and the sample as a whole showed an excess of manic over depressive episodes (10:1) and hypomanic over depressive episodes (5:1).

A phenomenologic breakdown of acute manic symptoms revealed a predominance of irritable (85%) rather than euphoric (15%) mood, and assaultive behavior was frequent (70%). Psychotic symptoms were present in only 15% of the sample. Other typical manic symptoms were seen in the following percentages of patients: impaired judgment, 100%; sleeplessness, 100%; grandiosity, 90%; pressured speech, 80%; flight of ideas, 75%; hyperactivity, 65%; and hypersexuality, 50%. No mixed manic states were observed.

The histories obtained from the 85 first-degree relatives revealed no family history of bipolar illness or schizophrenia. Six probands (30%) had one or more relatives with histories of depression.

DISCUSSION

Trauma to the CNS is a major cause of morbidity and mortality. The U.S. Health Interview Survey (18) estimated that there were 9,759,000 head injuries in

TABLE 2. Psychiatric Characteristics and Trauma Severity of Patients Who Became Manic After Closed Head Trauma

Patient	Index	Age (years)		Severity of Head Trauma	RDC Diagnosis	Number of Affective Episodes		
		At Trauma	At First Psychiatric Episode			Manic	Depressive	Hypomanic
1	23	16	18	Moderate	Schizoaffective, manic	4	1	0
2	47	41	42	Severe	Bipolar I	3	0	0
3	28	13	23	Severe	Bipolar I	5	0	0
4	42	40	41	Severe	Bipolar I	1	0	0
5	20	17	18	Mild	Bipolar II	0	2	8
6	41	39	39	Mild	Bipolar II	0	1	5
7	21	18	20	Mild	Bipolar II	0	2	1
8	45	24	28	Severe	Bipolar I	12	0	0
9	50	34	35	Severe	Bipolar I	8	0	0
10	42	40	41	Severe	Bipolar I	1	0	0
11	21	18	19	Moderate	Bipolar I	3	0	2
12	21	18	19	Severe	Hypomania	0	0	— ^a
13	22	20	20	Moderate	Bipolar I	8	0	8
14	28	23	25	Moderate	Bipolar I	4	0	2
15	28	5	17	Severe	Bipolar I	8	0	4
16	36	28	31	Severe	Schizoaffective, manic	4	4	0
17	52	26	34	Severe	Bipolar I	12	0	6
18	24	18	19	Severe	Bipolar I	5	0	0
19	42	36	36	Severe	Schizoaffective, manic	4	0	0
20	38	20	25	Severe	Bipolar I	18	0	12
Mean	33.5	24.7	27.5			4.9	0.5	2.7
SD	11.0	10.4	9.0					

^aChronic.

the noninstitutionalized population of the United States in 1975. Apart from the staggering physical sequelae, psychiatric consequences and their social repercussions may constitute a major problem in patients who survive. Fahey et al. (19) noted that of 22 civilian head injury patients, 17 had psychiatric symptoms 6 years after the injury but only two had been referred for psychiatric follow-up. The psychiatric symptoms cited in that study included affective outbursts, chronic irritability, epileptiform activity, and cognitive impairments.

Posttraumatic seizure disorders were found in 50% of our patients. This finding contrasts with the 5% overall prevalence of posttraumatic epilepsy reported in head injury victims (20). The predominance of temporal lobe epilepsy in our study is consistent with the well-known finding that temporal lobe epilepsy after closed head trauma is the type of epilepsy most frequently incriminated in overall psychological disturbances (21). Furthermore, it has been associated by Flor Henry with manic-depressive and schizoaffective disorder (21). Previous findings, along with our data, suggest that one of the predisposing factors in post-traumatic mania may be posttraumatic seizure disorders. Our sample displayed no family history of bipolar disorder, which *DSM-III* reports in organic affective disorders.

Whether head trauma is sufficient cause for subsequent affective syndromes or, possibly, a precipitant in an otherwise vulnerable individual requires further research. The findings of this study, however, do suggest that organic bipolar illness after head trauma may have distinct clinical-pathologic features; our

findings also support an etiologic association between head trauma and subsequent bipolar affective disorder in some patients.

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Diagnosis and Treatment of Mixed Mania

Steven K. Secunda, M.D., Alan Swann, M.D., Martin M. Katz, Ph.D.,
Stephen H. Koslow, Ph.D., Jack Croughan, M.D., and Sidney Chang, M.D.

In a study of 19 manic patients, the authors found that eight suffered from mixed mania, a condition in which depressive symptoms are found in the context of classic manic features. The presence of a mixed manic state predicted at least a slower and possibly a poor response to lithium therapy. The authors suggest that the definition of a subgroup of mixed manic patients might help to identify potential lithium-resistant patients.

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Although the new designation for manic-depressive illness—bipolar disorder—implies polar opposites, it has long been recognized that manic and depression can coexist in the same patient (1). In a longitudinal analysis of 20 bipolar inpatients, Carlson and Goodwin (2) observed "some depression" in 55%. Murphy and Beigel (3) reported that 28 of 30 manic inpatients had ratable depressive symptoms and that 17 of the 28 had moderate to severe depressive symptoms. Himmelhoch et al. (4) found that 31% of 84 newly admitted bipolar outpatients showed mixed features, and they noted a poorer response to lithium

treatment in their mixed manic group. Taylor and Abrams (5) in a large-scale retrospective study of 111 manic inpatients found no correlation between any clinical descriptor and response to lithium. All four of these studies, however, used only a simple cutoff score to rate the presence or absence of depression. Keller et al. (6), in an ongoing naturalistic clinical study of affective disorders, recently reported that 48% of 130 DSM-III-diagnosed bipolar I patients exhibited mixed features, and that those who did were less responsive to lithium treatment than the other bipolar patients.

As part of the NIMH Collaborative Program on the Psychobiology of Depression, 19 manic patients participated in a protocol similar to that used with the depressed patients (7, 8) in order for us to 1) study manic phenomenology in its own right and 2) provide a suitable control group for the larger depression study. The present paper focuses on the mixed manic state, its diagnosis and treatment. We describe a quantitative rating method for the diagnosis of mixed manic states, i.e., substantial concomitant depressive symptoms in the context of classic manic features. We also describe a test for determining whether this classification is predictive of response to lithium.

METHOD

We intensively studied all 19 manic patients: 12 were men with a mean age of 44.8 years (range, 23-62 years), and seven were women with a mean age of 43.9 years (range, 26-74 years). The background, rationale, and methodology of the overall study have been described previously (7-9).

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After a 14-day placebo washout period, lithium treatment began on day 15. Dose was initially titrated to maintain a level between 1.0 and 1.5 meq/liter and then adjusted subject to clinical response and side effects; 2 weeks after the start of lithium treatment, the patients' mean plasma lithium level was 1.14 meq/liter (range, 0.74–1.90 meq/liter).

To define the severity of illness of our 19 manic patients, we examined their past history and the present episode. The average patient had been sick for at least 10 years (as defined by the first hospitalization), had four and a half previous hospitalizations for an affective illness before the present one, and had previously suffered approximately four manic episodes and five depressive episodes. This was the first manic episode for two patients.

For the present episode, the average manic patient was ill for 7 weeks before admission and entered the hospital at or close to the peak of his or her manic symptoms. The Global Adjustment Scale (GAS) from the Schedule for Affective Disorders and Schizophrenia (SADS) (10), an overall measure of ability to function that assesses limitations and positive coping mechanisms, was administered to each patient.

The *DSM-III* criteria for bipolar disorder, mixed (296.6x), include 1) the full symptomatic picture of both manic and major depressive episodes intermixed or rapidly alternating every few days, and 2) depressive symptoms that are prominent and last at least a full day. In the present study, patients were diagnosed as mixed manic only if they showed concomitant depressive symptoms in the context of classic manic features. The criterion of "rapidly alternating every few days" was eliminated because of potential overlap with the research category of rapid cycling. In addition, the second criterion of "prominent depressive symptoms" was quantified by the use of the nurse-rated Affective Disorder Rating Scale, depression factor (11), and the physician-rated Hamilton Rating Scale for Depression (12).

The nurse-rated depression factor was used as our initial screening device. This factor, which measures core depressive symptoms, comprises five items: sadness, guilt, self-criticism, suicide, and helplessness. Subjects were initially evaluated on the basis of having a depression factor score >1.5 on at least one of the three pretreatment days (day 3, 10, or 15). The mean \pm SD depression factor scores on day 15 were 2.0 (± 0.76) for the mixed group and 1.1 (± 0.25) for the pure manic group. Confirmation of depression was verified with the Hamilton depression scale. A Hamilton score >15 was required during the pretreatment period. The mean Hamilton scores on day 15 were 17.0 (± 7.8) for the mixed group and 5.1 (± 2.8) for the pure manic group. Finally, for a subject to be judged mixed manic, *DSM-III* criteria for a major depressive episode had to be met.

A multivantaged approach to measuring overall manic phenomenology and rating change that combined several observational scales from interview, vid-

eo, and ward situations was also used. A new measuring instrument, the Manic Diagnostic and Severity Scale, was used to integrate the various subscales employed (9).

To test hypotheses that require recovery or nonrecovery criteria, a procedure for classification was derived that made use of both doctors' and nurses' overall judgments of outcome in a set of four quantifiable indexes. The overall severity of the specific manic state and the severity of the general psychopathology were utilized in deriving these categorical outcome criteria (8).

RESULTS

Using the selection criteria, we identified eight (44%) mixed manic patients and 10 (56%) pure manic patients for the present episode. One subject spontaneously recovered by day 15 and was not included in this analysis, and another subject (mixed manic) decompensated and was removed from the study before treatment began. No significant differences were found between the mixed and pure manic groups on the pretreatment Manic Diagnostic and Severity Scale score (day 10) (Wilcoxon test, $p < .4$), in overall psychopathology as measured by the SADS-GAS, in SADS ratings of psychoticism, or in treatment plasma lithium levels throughout the study.

Using the categorical outcome criteria for response versus nonresponse, we found that nine of 10 pure manic patients and only two of the seven mixed manic patients responded to lithium therapy within the 25-day treatment period (Fisher's exact test, $p = .03$). Although more women than men were classified as mixed manic, this finding was not significant (Fisher's exact test, $p = .07$). Furthermore, being a woman did not by itself predict a poor response to lithium therapy (Fisher's exact test, $p = .1$).

DISCUSSION

The prevalence of mixed mania reported in previous studies (2–5) that used a simple global rating of depression has ranged from 30% to 60%. Using *DSM-III* criteria, we found that 44% of our manic patients showed substantial depressive pathology. We also found that the presence of a mixed manic state predicted a poor response to lithium therapy. Because our total treatment study period was only 25 days, our mixed manic patients may have been slow responders rather than nonresponders. Keller et al. (6) reported that the mean time to recovery was 5 weeks for their pure manic patients and 14 weeks for their mixed group; however, their lithium doses and schedules were not standardized but left to the discretion of the treating physicians.

Our finding that female manic patients were more likely to have depressive symptoms than their male

counterparts was comparable to the finding of Himelchock et al. (4) that 37.0% of their female patients but only 23.7% of their male patients were diagnosed as mixed manic-depressive. Krishnan et al. (13), studying abnormal cortisol suppression, reported that nine out of 10 consecutively admitted patients who met the criteria for a mixed bipolar state were women.

It has been reported (14) that 10%–20% of manic patients are lithium refractory, and investigators have sought to find alternative treatments. Okuma et al. (15) first reported that the anticonvulsant drug carbamazepine has both antimanic and prophylactic effects on bipolar illness. More recently, Post et al. (16) reported on the successful response of lithium nonresponders to carbamazepine in both acute and maintenance treatment phases. Alternatives for lithium treatment include other anticonvulsant medications such as dipropylacetamide and sodium valproate as well as the benzodiazepine clonazepam (17). Some of these studies considered the presence or absence of rapid cycling, but none noted whether a mixed manic state was found. An anecdotal report (18) noted a favorable response to clonidine in one mixed bipolar patient.

This study demonstrates that mixed manic patients who showed substantial depressive pathology at baseline were significantly less likely to respond to lithium therapy than pure manic patients. The lack of response to lithium by the mixed manic group was independent of the initial severity of manic symptoms. No other historical or baseline clinical finding differentiated this treatment response. This study indicates that future work on the treatment of lithium-resistant patients should delineate the mixed state as a separate subgroup of manic patients.

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Ethological Study of Facial Behavior in Nonparanoid and Paranoid Schizophrenic Patients

Roger K. Pitman, M.D., Bryan Kolb, Ph.D.,
Scott P. Orr, Ph.D., and Man Mohan Singh, M.D.

This investigation addressed the question of affective disturbance in schizophrenia by applying quantitative measurement techniques to patients' facial behavior. The subjects were medication-free male inpatients: nine nonparanoid and six paranoid schizophrenic patients and 12 drug- or alcohol-abuse rehabilitation control patients. Two judges scored the subjects' behavior, which was recorded on videotape, according to a system that included 16 different types of facial movements. Eye blinks, eye contact, and words spoken were also scored. Compared to the control patients, the nonparanoid schizophrenic patients spoke significantly fewer words and had significantly less eye contact, while the paranoid schizophrenic patients had significantly fewer eyebrow and lower facial movements.

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The major studies of affect in schizophrenia to date have employed rating scales (1-3). An alternative to rating scales is the ethological method, which involves describing the components of animal or human behavior in a manner relatively free of theoretical preconceptualizations and scoring their occurrence in live or recorded behavioral samples. This approach has had some application to psychiatric situations in general (4-6) and to schizophrenia in particular (7-11). In view of the role of facial behavior in the expression and communication of human emotion (12), we applied ethological scoring techniques to the facial behavior of schizophrenic patients in an attempt to more objectively characterize the nature of schizophrenic affective disturbance. Other investigators have independently urged the ethological approach to studying affect in schizophrenia (13).

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METHOD

Subjects were recently admitted male inpatients at the Memphis Veterans Administration Medical Center during 1979-1980. All were kept free of psychotropic medications and drugs for at least a week before being interviewed. None showed overt clinical signs of extrapyramidal dysfunction (Parkinsonism or dyskinesia) at the time of the study. The index group consisted of 15 patients who met the Research Diagnostic Criteria (RDC) (14) for schizophrenia on the basis of the consensus of two Board-certified psychiatrists who conducted structured interviews. Six index patients met the RDC for paranoid type and nine did not. Subsequent review of records of the interviews and further information obtained during the course of hospitalization indicated that of the six patients diagnosed as paranoid schizophrenic according to the RDC, five also met *DMS-III* criteria for schizophrenia, paranoid type; one patient was classified as having schizoaffective disorder. Of the nine index patients diagnosed as nonparanoid schizophrenic according to the RDC, eight also met *DMS-III* criteria for schizophrenia, type other than paranoid; while one was classified as having schizoaffective disorder. The control group consisted of 12 patients from the alcohol- or drug-dependence rehabilitation programs, none of whom had any psychotic or active affective disorder. The control group was matched with the schizophrenic group for age, educational level (highest grade completed), and racial composition. The rationale for choosing this control group was that its members had a comparable drug-free inpatient status but were expected to manifest affect approaching the normal.

The mean \pm SD ages for the groups were as follows: control patients, 30.0 ± 6.4 years; nonparanoid schizophrenic patients, 26.0 ± 4.3 years; and paranoid schizophrenic patients, 30.3 ± 5.9 years. The control patients had a mean of 11.6 ± 2.1 years of education; the nonparanoid schizophrenic patients, 10.6 ± 2.2 years; and the paranoid schizophrenic patients, 12.7 ± 2.9 years. The control group consisted of four white and eight black subjects; the nonparanoid schizophrenic group, two whites and seven blacks; and the paranoid schizophrenic group, two whites and four blacks.

TABLE 1. Measures of Facial Behavior for Nine Nonparanoid and Six Paranoid Schizophrenic Patients and 12 Control Patients During a 5-Minute Interview Period

Behavior	Control Patients		Schizophrenic Patients				F (df=2,24)	p
			Nonparanoid		Paranoid			
	Mean	SD	Mean	SD	Mean	SD		
Eyebrow movements	14.6	8.3	9.0	11.0	3.5	5.9	3.31	.05 ^a
Eye closures	2.0	3.3	3.3	3.9	4.0	5.5	<1.00	n.s.
Smiles	1.7	1.5	2.9	2.3	4.3	7.8	<1.00	n.s.
Other lower facial movements	18.1	8.2	12.4	3.2	8.3	6.8	4.74	<.02 ^a
Glances	41.6	6.5	30.0	10.9	21.0	9.3	11.64	<.001 ^b
Eye blinks	127	56.0	107	70.0	194	143.0	2.32	n.s.
Duration of eye contact (sec)	184	55.0	105	58.0	230	40.0	10.83	<.001 ^c
Words spoken by patient	601	130.0	221	116.0	455	92.0	26.03	<.001 ^c
Words spoken by interviewer	175	53.0	222	64.0	196	101.0	1.20	n.s.

^aSignificant difference between the control patients and the paranoid patients; for this and following comparisons, Scheffé's a posteriori comparisons significant at $p < .05$ level.

^bSignificant difference between the control patients and both the nonparanoid and paranoid patients.

^cSignificant difference between both the control and paranoid patients and the nonparanoid patients.

Separate analyses of variance (ANOVAs) for the demographic variables (chi-square test for the racial data) revealed no significant differences.

The nature of the procedure was fully explained before we obtained written informed consent, including consent for videotaping, from each subject. Each patient then underwent an open-ended, nondirective psychiatric interview performed by one of us (R.K.P.), with a close-up recording made of the patient's face by a camera located behind the interviewer. The interviewer attempted to maintain the same format across patients, reacting naturally to their communications and facilitating their talking as much of the time as possible. The first 5 minutes of each interview were reviewed and scored in scrambled order in real time by judges who were blind to the patient's identity and group membership.

One of us (B.K.) and an associate independently scored each patient's facial behavior (without using the audio portion of the interview) according to an ethological scoring system previously reported (15). Sixteen different individual facial behaviors were scored within five categories, as follows: eyebrow movements (raise brows, raise one brow, knit brows), eye closures (half-close, loose close, tight close), smiles (slight, wide, open-mouthed), other lower facial movements (tighten lips, lower mouth corners, roll lips in, lips out, bite lip, tongue visible), and glances at the interviewer. Although this list of movements is not exhaustive, it has been found to adequately describe the range and frequency of facial movements of patients previously studied (15). In addition, one of us (S.P.O.) and an associate scored eye blinks and eye contact with the interviewer. Interrater reliabilities (intraclass correlation coefficients) (16) were as follows: eyebrow movements, .84; eye closures, .49; smiles, .59; other lower facial movements, .55; glances at the interviewer, .83; eye blink, .94; and eye contact, .95. One of us (S.P.O.) subsequently rescored eye contact, divided into the time when the patient was speaking and the time when he was listening. Finally, the number of words spoken

by the patient and the interviewer were counted from transcripts.

RESULTS

A multivariate ANOVA for the means of the three patient groups (control, nonparanoid schizophrenic, and paranoid schizophrenic), which used the eight patient-behavior dependent variables in table 1, demonstrated a significant difference ($F=3.61$, $df=16,32$; $p=.001$; Wilks's criterion). Table 1 presents the means and univariate ANOVAs and significant a posteriori comparisons for the individual dependent variables.

The mean \pm SD ratios of percentage of eye contact while talking to percentage of eye contact while listening for the three groups were as follows: control, $.60 \pm 0.21$; nonparanoid schizophrenic, $.31 \pm 0.23$; and paranoid schizophrenic, $.83 \pm 0.30$. ANOVA of these ratios demonstrated a significant difference ($F=7.26$, $df=2,24$, $p<.01$). Scheffé's a posteriori comparisons indicated that the mean ratio for the paranoid patients was significantly higher than that for the nonparanoid patients.

Because of the special attention that has been paid to brow movements in human nonverbal communication (17, 18), the category of eyebrow movements was subjected to a more detailed examination. The great majority of eyebrow movements were raises of both brows simultaneously. A total of 230 of these eyebrow raises were counted in the 12 control patients; all 230 were speech-related; i.e., they occurred while the subjects were speaking and served as conversational markers, as defined by Ekman (18). Of the 23 eyebrow raises counted in the six paranoid schizophrenic patients, 22 were speech-related. It was only in the nonparanoid schizophrenic patients that any degree of non-speech-related eyebrow raises occurred; of 97 eyebrow raises in this group, 60 were speech-related and 37 were not. Twenty-four of these non-speech-related eyebrow raises occurred in one patient and 10

in another; in both patients these eyebrow movements appeared autistic, i.e., entirely unrelated to the patient-interviewer interaction. Of 38 knit-brow movements counted in the control patients, 30 were speech-related and six occurred in an appropriate context while the subjects were listening. All three knit-brow movements in the paranoid schizophrenic patients were speech-related; of 33 knit-brow movements in the nonparanoid schizophrenic patients, 18 were speech-related and 15 were not. Of the 15 non-speech-related knit-brow movements in the nonparanoid schizophrenic patients, 13 occurred in the same two patients who had shown the autistic eyebrow raises; in these patients the knit-brow movements also appeared autistic.

DISCUSSION

Analysis of the results indicates that the dependent variables employed in this study were reliable and able to distinguish among the two groups of schizophrenic patients and the control patients. The nonparanoid patients spoke less and looked less at the interviewer. It has been reported that among nonverbal behaviors, low rates of speech and eye contact accounted for two-thirds of the variance in judged social skill in a group of psychiatric patients (19). The paranoid patients, on the other hand, spoke to the interviewer nearly as much as the control patients did and had slightly more eye contact. The combination of a high rate of eye contact and low rate of glances in the paranoid patients amounted to staring at the interviewer. However, while the paranoid patients spoke a good deal, their talking was accompanied by fewer nonverbal expressions. Thus, the paranoid schizophrenic patients were distinguished by a low rate of nonverbal expressivity, while the nonparanoid schizophrenic patients were distinguished by a low rate of verbal expressivity, plus the appearance of out-of-context or autistic nonverbal movements.

Ethological theorists have advanced models of human social interaction that classify behavior into three major categories: bonding, aggression (or dominance), and flight (or submission) (7, 20, 21). The low overall eye contact and low ratio of eye contact while talking to eye contact while listening in the nonparanoid schizophrenic patients we studied is suggestive of flight (7, 22); the high overall eye contact and the high ratio of eye contact while talking to eye contact while listening, but fewer eyebrow raises, in the paranoid schizophrenic patients is suggestive of aggression in the absence of bonding (17, 22).

A high rate of eye blinking has previously been reported in schizophrenic patients and has been attributed to a hyperdopaminergic state (23, 24). The group main effect for number of eye blinks approached but did not achieve significance ($p=.12$). Inspection of the data in table 1 reveals that the mean number of blinks of the nonparanoid schizophrenic patients was slightly lower than that of the control patients, while the mean

for the paranoid patients was considerably higher. Of the five subjects with a blink rate of greater than 40 per minute, three were paranoid schizophrenic patients, including those with the two highest rates of 75 and 60 blinks per minute. This is of interest in view of the suggestion that the paranoid subtype of schizophrenia may be the one most likely to be characterized by hyperdopaminergia (25). The higher mean blink rate in the paranoid schizophrenic group also helps to discount the possibility that the low rate of nonverbal expressiveness which characterized this group may have been caused by lingering Parkinsonian effects of neuroleptics that were taken before the onset of the drug-free period, because blink rate would be expected to be low in drug-induced Parkinsonism (23, 24).

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The Prognostic Validity of DSM-III Axis IV in Depressed Inpatients

Mark Zimmerman, B.A., Bruce Pfohl, M.D., William Coryell, M.D., and Denle Stangl, M.A.

DSM-III suggests that axis IV should have prognostic value—that patients with higher scores will have a better outcome than patients with low ratings. The authors used axis IV to assign scores to 130 depressed inpatients and examined these scores in association with the patients' course during the index hospitalization and at 6-month prospective follow-up. Higher axis IV scores were associated with more depressive symptoms on hospital discharge, but they did not predict follow-up outcome. These results are consistent with other studies of the prognostic value of ratings of psychosocial stress and indicate that, at least for depression, there is little empirical support for DSM-III's suggestion that stress is a favorable prognostic sign.

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In our previous report on the validity of DSM-III axis IV (1), we found that depressed patients with higher axis IV scores were characterized by lower rates of abnormal dexamethasone suppression test (DST) results, a higher morbid risk for alcoholism among first-degree relatives, a greater frequency of personality disorders, and a greater likelihood of attempted suicide during their index episode. In the present report we

focus on the predictive validity of axis IV and examine the relationship between axis IV ratings and patients' response to treatment while in the hospital and patients' course during a 6-month prospective follow-up. DSM-III suggests that higher axis IV (severity of psychosocial stressors) scores will be associated with a better prognosis.

METHOD

The patients have been described in detail in our previous report on the validity of axis IV (1). Briefly, over a 2-year period we recruited for study a consecutive series of inpatients 18 years of age or older with DSM-III-diagnosed major depressive disorder. Exclusion criteria were limited to the medical or pharmacologic conditions that might invalidate the results of the DST (2-4). We used DSM-III axis IV to rate 130 patients whom we assessed with a semistructured life events interview (5). The majority of the 130 patients were women (71.5%, N=93), were high school graduates (81.5%, N=106), and had had one or more previous psychiatric hospitalizations (80.8%, N=105). At the time of admission, 51 (39.2%) of the patients were married, 33 (25.4%) were single, 28 (21.5%) were divorced, nine (6.9%) were separated, and nine were widowed.

We completed the 17-item Hamilton Rating Scale for Depression (6), the Beck Depression Inventory (7), and the Global Assessment Scale (GAS) (8) within 1 week of admission and weekly thereafter until discharge. In the present report, improvement was defined as a decrease of at least 50% from admission to

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discharge in Hamilton scale score, and recovery was defined as a discharge Hamilton scale score of 6 or less (9).

Patients received their physician's choice of treatment. In a naturalistic design such as ours, the speed and degree of improvement tend to be reciprocally related with medication dose and trial duration. Moreover, the aggressiveness of treatment is, in part, dictated by the treatment received before hospitalization. Thus, we did not attempt to control for the quantity of pharmacotherapy. We did, however, divide patients into those who had and had not received ECT.

Raters blind to the axis IV ratings contacted the patients 6 months after entry into the study and quantified their psychopathology in a fashion resembling that developed by the Collaborative Program on the Psychobiology of Depression of the Clinical Research Branch, National Institute of Mental Health (10). For each week of the follow-up, raters determined whether patients had felt like their usual, normal selves and rated the presence or absence of the eight symptoms from *DSM-III* part B criteria for major depressive disorder for each postdischarge week. To do this, the raters asked about change points, dates when definite improvement or worsening took place. They then assigned the intervening weeks a symptom rating on a 4-point scale. A week without depressive symptoms was assigned a score of 1, whereas the presence of 1 or 2 criterion depressive symptoms resulted in a score of 2. A score of 3 reflected the presence of 3 or 4 criterion symptoms, and the presence of 5 or more symptoms was scored 4. The raters also determined the type and amount of treatment received following discharge from index hospitalization and completed the Hamilton scale, the Beck inventory, and the GAS for the week before the follow-up interview.

To maximize use of outcome data, we determined the mean symptom rating across all weeks of the follow-up for each patient and calculated the mean of these values for the high- and low-stress groups. We then considered outcome using four different definitions of "sustained recovery." According to the convention adopted by the Collaborative Program on the Psychobiology of Depression, sustained recovery required a period of at least 8 consecutive weeks with no more than one or two depressive symptoms to a mild degree (11). The second definition of sustained recovery required that the patient also feel like his or her usual self during the 8 weeks in which he or she had only one or two depressive symptoms. Third, consistent with our previous reports on the 6-month outcome following ECT (12, 13), we defined recovery as an 8-week period entirely free of symptoms. Finally, we defined sustained recovery as an 8-week period during which the patient felt like his or her usual self, regardless of the level of depressive symptoms.

Reliability of our follow-up interview was assessed in two ways (14). Twenty-one depressed patients were interviewed once a month after their discharge from

the hospital until their scheduled 6-month follow-up interview. The monthly interviews followed the format described here for the 6-month interview. Audiotapes of these interviews were rated to assess reliability in an observer/rater paradigm. Next, an independent rater interviewed the patient 6 months after the index admission and assessed symptoms for the entire post-discharge period. Thus, we examined the test-retest reliability of follow-up assessments by comparing information obtained from the monthly interviews with the data collected at the 6-month interview. The observer-rater paradigm showed excellent agreement for audiotape ratings of the monthly interviews, and there was generally good agreement between the monthly and 6-month interviews (14).

In our previous report we divided the patients into three groups on the basis of their axis IV ratings. However, in the present study we planned to examine the prognostic validity of axis IV separately for patients who had and had not received ECT during the index hospitalization, and the sample sizes became very small when we divided the sample into three groups. Therefore, we classified the patients into low-stress ($N=60$) and high-stress ($N=70$) groups depending on whether their axis IV rating was above or below the mean \pm SD value for the entire group (4.4 ± 1.3). In *DSM-III* terminology, the low-stress group had mild to moderate stress, whereas the high-stress group had severe to extreme stress. Of note, three of the four significant correlates of axis IV found when we divided the patients into three groups were still apparent with the two-group subdivision. That is, in contrast to the patients with low-stress ratings (axis IV score of 1–4), patients with higher axis IV scores were characterized by lower rates of DST nonsuppression (21.4% [$N=18$] versus 36.7% [$N=22$]; $\chi^2=3.68$, $df=1$, $p<.06$), a higher morbid risk of alcoholism (13.5% versus 5.7%; $\chi^2=11.04$, $p<.001$), and a greater frequency of personality disorders (58.4% versus 43.8%; $\chi^2=1.74$, $n.s.$). The likelihood of attempted suicide during the index episode was similar in the low- and high-stress groups (28.3% [$N=17$] versus 31.4% [$N=22$]; $\chi^2=0.15$, $n.s.$).

We also examined axis IV as a continuous variable and calculated Pearson correlation coefficients between axis IV and continuous independent variables such as Hamilton scale, Beck inventory, and GAS scores.

RESULTS

Patients with low axis IV scores were more likely to have received ECT (40.0% [$N=24$] versus 24.3% [$N=17$]; $\chi^2=3.69$, $df=1$, $p<.06$). The data in table 1 show that hospital duration was associated with axis IV only for the patients not treated with ECT; however, axis IV scores accounted for less than 2% of the variance of hospitalization duration ($r=.12$). Twenty-six patients (12 with low stress, 14 with high stress)

TABLE 1. Hospital Course of 130 Depressed Patients With Low or High Stress^a Who Were or Were Not Given ECT

Variable	Low Stress			High Stress			t	df	Significance
	Number of Patients	Mean	SD	Number of Patients	Mean	SD			
Patients given ECT (N=41)									
Number of days hospitalized	24	43.0	16.5	17	48.8	20.2	1.01	39	n.s.
Hamilton scale score									
Admission	24	23.1	5.9	17	23.7	4.7	0.36	39	n.s.
Discharge	24	7.2	6.4	17	11.6	7.9	1.98	39	p<.10
Beck inventory score									
Admission	22	31.2	10.5	14	32.9	14.1	0.42	34	n.s.
Discharge	22	8.8	6.8	14	17.0	13.0	2.17	34	p<.05
GAS score									
Admission	24	38.0	9.0	17	36.9	5.5	0.51	39	n.s.
Discharge	24	60.7	9.3	17	55.3	10.8	1.71	39	p<.10
Patients not given ECT (N=89)									
Number of days hospitalized	36	16.8	9.4	53	22.2	16.6	1.96	87	p<.10
Hamilton scale score									
Admission	24	21.0	6.8	39	25.3	5.0	2.85	61	p<.01
Discharge	24	8.3	6.7	39	13.6	7.8	2.77	61	p<.01
Beck inventory score									
Admission	23	24.3	9.5	37	31.7	9.8	2.87	58	p<.01
Discharge	23	9.1	6.7	37	16.4	10.6	3.27	58	p<.01
GAS score									
Admission	24	39.7	10.3	39	37.8	6.9	0.82	61	n.s.
Discharge	24	60.2	11.8	39	55.1	11.0	1.73	61	p<.10

^aLow stress=DSM-III axis IV score of 1-4; high stress=DSM-III axis IV score of 5-7.

were discharged before we completed a second set of Hamilton scale, Beck inventory, and GAS ratings and thus were excluded from the analyses of response during hospitalization.

High- and low-stress patients treated with ECT were equally symptomatic at admission (table 1), and all of the correlations between axis IV and the pre-ECT symptom scores were less than .08. At discharge the high-stress group was more depressed than the low-stress group (table 1), and axis IV scores accounted for 10% of the variance of discharge Hamilton scale scores ($r=.32$, $p<.05$) and Beck inventory scores ($r=.32$, $p<.05$). The correlation between axis IV and GAS scores failed to reach significance ($r=-.19$). There was a nonsignificant trend for fewer high-stress patients than low-stress patients treated with ECT to improve during their hospitalization (58.8% [$N=10$] versus 75.0% [$N=13$]; $\chi^2=1.20$, n.s.), and fewer were recovered at discharge (29.4% [$N=5$] versus 50.0% [$N=12$]; $\chi^2=1.74$, n.s.).

In patients not treated with ECT, higher axis IV scores were associated with greater symptom severity at both admission (Hamilton scale, $r=.29$, $p<.01$; Beck inventory, $r=.38$, $p<.001$; GAS, $r=-.08$, n.s.) and discharge (Hamilton scale, $r=.29$, $p<.01$; Beck inventory, $r=.33$, $p<.001$; GAS, $r=-.20$, $p<.06$). Axis IV was still significantly correlated with the discharge ratings even after we controlled for admission scores (Hamilton scale, partial $r=.25$, $p<.05$; Beck inventory, partial $r=.24$, $p<.05$; GAS, partial $r=-.20$, $p<.07$). In addition, after we controlled for admission symptom severity with an analysis of covariance, discharge Hamilton scale and Beck inventory ratings of the high-stress group remained significantly

TABLE 2. Rehospitalization and Recovery Rates During 6-Month Follow-Up in 115 Depressed Inpatients^a With Low or High Stress^b

Outcome	Low Stress (N=52)		High Stress (N=63)		χ^2 (df=1) ^c
	N	%	N	%	
Rehospitalization	12	23.5	21	33.9	1.44
Recovery sustained for 8 weeks					
1 or 2 depressive symptoms	29	55.8	33	52.4	0.13
1 or 2 depressive symptoms and back to normal self	22	42.3	24	38.1	0.21
No depressive symptoms	17	32.7	15	23.8	1.12
Back to normal self	24	46.2	27	42.9	0.13

^aThe two patients who committed suicide were included in the unrecovered group. Percents for the rehospitalization analysis, however, are based on $N=113$: 51 in the low-stress group and 62 in the high-stress group.

^bLow stress=DSM-III axis IV score of 1-4; high stress=DSM-III axis IV score of 5-7.

^cAll differences were nonsignificant.

higher than the ratings in the low-stress group. Significantly fewer of the high-stress patients were recovered at discharge (23.1% [$N=9$] versus 50.0% [$N=12$]; $\chi^2=4.85$, $df=1$, $p<.05$), and a similar, nonsignificant trend was found for rates of improvement (43.6% [$N=17$] versus 62.5% [$N=15$]; $\chi^2=2.13$, n.s.).

We successfully followed up 113 (86.9%) of the 130 patients. Three patients died during the follow-up interval (two by suicide), 11 patients could not be located, and three refused to be interviewed. The data in table 2 indicate that there were nonsignificant trends for the high-stress group to be more frequently hospitalized and less frequently recovered during the follow-up. High- and low-stress patients did not signifi-

cantly differ by mean weekly follow-up score (2.8 ± 1.0 versus 2.5 ± 1.1 , $t=1.26$, n.s.), 6-month Hamilton scale score (10.3 ± 9.2 versus 8.2 ± 7.9 , $t=1.31$, n.s.), 6-month Beck inventory score (16.6 ± 14.1 versus 12.2 ± 12.5 , $t=1.72$, $p<.10$), or 6-month GAS score (59.2 ± 17.8 versus 61.7 ± 17.9 , $t=0.75$, n.s.), although all the trends indicated greater symptom levels in the high-stress group.

DISCUSSION

In its description of axis IV, *DSM-III* noted that "an individual's prognosis may be better when a disorder develops as a consequence of a severe stressor than when it develops after no stressor or a minimal stressor." The results of the present study are not consistent with this prediction. In fact, we found that high axis IV scores were significantly associated with poorer hospital outcome and that there was a similar nonsignificant trend in the follow-up results. A review of the literature examining the prognostic validity of precipitating stress in depressed patients suggests that our results are not anomalous.

Ten studies (15–24) have examined the relationship between precipitating stress and ECT outcome. Thomas (15) found that patients with reactive depression were one-half as likely as those with nonreactive depression to recover or be much improved following ECT, and Rose (16) reported that the presence of a precipitating stress was associated with poor outcome 1 and 3 months after ECT treatment. Hamilton and White (17) found that the change in Hamilton scale scores for pre- to post-ECT was smaller in patients with definite reactive depression than in those with definite endogenous depression. Havens (18) indicated that poorer outcome during the 6 months after the completion of the course of ECT was significantly associated with the loss of close relatives within 2 years before hospital admission. Carney et al. (19) also found that the absence of psychosocial stress was associated with better outcome 3 months after ECT. In contrast, four studies (20–23) failed to find an association between stress and ECT outcome, and one (24) found that patients with situational depression had a better response to ECT than those with nonsituational depression. Thus, in five studies, precipitating stress predicted a poorer ECT response, four studies failed to find an association, and one study supported the *DSM-III* position that a precipitant is a favorable prognostic sign.

Seven studies of depressed patients (25–31) failed to find an association between response to pharmacotherapy and precipitating stress. Kiloh et al. (32) found that the presence of a precipitant was associated with poorer outcome; Tyrer et al. (33) found the opposite. Prusoff et al. (34) reported that response to amitriptyline was superior in situational than nonsituational depression, although combined pharmacotherapy-psychotherapy treatment produced similar responses.

Follow-up studies are equivocal in their support for *DSM-III*'s thesis that the outcome of precipitated depression is better than the outcome of unprecipitated depression. Hirschfeld (35) reported that patients with situational depression recovered more quickly than those with nonsituational depression, although the overall rate of recovery was similar 1 year after intake. Monroe et al. (36) found that high life event scores were associated with poor 6-month outcome in patients with endogenous depressive symptoms but not in patients who lacked these symptoms, whereas Paykel et al. (37) found that life event scores did not predict 10-month follow-up outcome. In contrast, Copeland (38) found that patients whose index episode followed a stressful event were significantly less likely "to feel mainly well" during a 5-year follow-up interval. Finally, two follow-up studies of untreated depressed patients (21, 39) failed to find that precipitated depression had a better outcome. In fact, Huston and Locher (21) reported that the time until recovery was longer in precipitated depression.

Although these studies differed in their definitions of depression, precipitating stress, and recovery, it is clear that, at least for depressive disorder, there is little empirical support for *DSM-III*'s suggestion that precipitating stress is a favorable prognostic sign.

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The Alaska Mental Health Lands

Jerry L. Schrader, M.D.

The Alaska mental health program is endowed with a 1-million-acre trust fund. A coalition of groups that make up the mental health constituency of the state united in a lawsuit to establish the trust. The history of this legacy, the struggle to realize its benefits, its current status, and some of its psychopolitical significance are discussed.
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It has been the policy of the federal government to grant land to territories and states for schools and other public purposes. Although we are familiar with land grant colleges, few of us realize that land grants were made to the states of Idaho, Oklahoma, South Dakota, Utah, and Wyoming "specifically to provide the means for the care of the insane" (1). These land grants were substantial: 100,000 acres in Utah, 30,000 in Wyoming, 200,000 in Oklahoma, and 50,000 in Idaho. The states were given minimal directions for the use of these lands. My review of their statehood acts (2) confirmed that the states did receive these land grants. However, the act for each of the states includes language which leaves considerable doubt that the land grants have survived. For example, in Wyoming, the law provides that "none of the lands granted by this act shall be sold for less than 10 dollars per acre."

My attempt to clarify the current status of mental health lands in these states met with mixed results. The Idaho Lands and Resources Department stated that it has "charitable lands," which include a grant for the state hospital. All of these lands are administered separately from general state lands. The South Dakota Department of School and Public Lands and the Department of Charities and Corrections were unaware of any mental health lands in their state. The Utah Department of Natural Resources stated that 18,000 acres of an original 50,000-acre mental health land grant remain. The Wyoming State Division of Public Lands was aware of a 30,000-acre land grant for an insane asylum, but some of the acreage was sold and some of it has never been obtained from the federal government. No information was obtained from Oklahoma.

The existence of land grants for the care of the mentally ill has not been generally recognized by the mental health constituency. The term "mental health" was not in use when most states came into existence. As a consequence, land grants to the states may have been referred to as grants to specific institutions or asylums. Alaska, because of its recent statehood, is an exception. A description of Alaska's experience with the mental health lands may serve to increase public awareness of the existence of these land grants in other states.

THE ALASKA LAND GRANT

In 1956 the Congress, through Public Law 830 (3), established a 1-million-acre land grant to provide Alaska the means to care for its mentally ill. The language of the law is uniquely strong and clear. Section 202(e) of the Act specifically provides:

All lands granted to the Territory of Alaska under this section, together with the income therefrom and the proceeds from any dispositions thereof, shall be administered by the Territory of Alaska as a public trust and such proceeds and income shall first be applied to meet the necessary expenses of the mental health program of Alaska. Such lands, income and proceeds shall be managed and utilized in such a manner as the Legislature of Alaska may provide. Such lands, together with any property acquired in exchange therefore or acquired out of the income or proceeds therefrom, may be sold, leased, mortgaged, exchanged or otherwise disposed of in such manner as the Legislature of Alaska may provide in order to obtain funds or other property to be invested, expended or used by the Territory of Alaska. The authority of the Legislature of Alaska under this subsection shall be exercised in a manner compatible with the conditions and requirements imposed by other provisions of this Act. (italics added)

In spite of this clear statement of purpose, the policy of the State of Alaska has been to manage these lands and other trust lands without regard for their trust status. The mental health lands, which were selected during the late 1950s, are near municipalities and in high-resource areas. As a consequence they are extremely valuable and are much in demand by municipalities, Alaskan Native corporations, and state agencies. It has been the state's policy to allow leases on these lands at less than market value, to allow exchanges of these lands, to allow state agencies to "manage" portions of the lands for their own internal

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benefit, and to maintain a "rough" accounting of the income from the lands.

THE LAWSUIT

In 1978 the legislature of Alaska, working closely with the office of the governor, made this policy part of a state law (4). They "redesignated and disposed" of all trust lands (mental health, university, and school lands). In exchange, they provided that a percentage of the state revenue derived from the lands could be placed in a trust fund for the original purposes. However, no funds were ever appropriated for these purposes. The Board of Regents of the University of Alaska immediately sued the state to obtain control of the university trust lands and to assess the damages. The Alaska Supreme Court ruled in favor of the university on appeal in February 1981 (5), recognizing in this case the state's right to take specific tracts of land, but ruled that the trust must be appropriately compensated.

The mental health constituency, lacking an entity similar to the board of regents, was slower to react. The board of regents could fund their lawsuit; the mental health constituency was without funds. At first, attempts were made by the Alaska Mental Health Association, strengthened by the strong position of the Alaska Supreme Court in the university case, to obtain a resolution of the problem through the legislature. No relief was possible, and the association was told that its reasoning was irrational and its demands were unrealistic. With the assistance of a public-spirited attorney, a class action suit was filed in the Alaska Superior Court on Nov. 26, 1982.

On June 14, 1983, the Superior Court ruled in favor of the mental health land trust. Judge Warner W. Taylor, in a strongly worded opinion, quoted from a landmark U.S. Supreme Court case (6) which stated, in part, that the requirement of the Senate Committee on the Territories for restrictions on trust lands "sprang from its fear that the trusts would be exploited for private advantage." Judge Taylor ordered the State of Alaska to account for the value of the lands removed from the trust.

The state was slow to respond to this order. It immediately appealed to the Alaska Supreme Court, which declined to hear the case at this stage. In December 1983, 6 months after the Superior Court ruling, a hearing was held which provided the state an opportunity to explain the delay. The court then gave the state a deadline of March 31, 1984, for compliance. The state responded with incomplete information, citing the difficulty of appraising such a large acreage. A request by the mental health attorney for an injunction against further state land transfers until the state complied was denied, but it served the purpose of forcing the state to accept a stipulated agreement and a request by both parties to refer the matter to the Alaska Supreme Court for a decision.

The Alaska Supreme Court accepted the case on appeal in May 1985. Oral arguments were presented to the court in August 1985, and the court's decision, which was published on Oct. 4, 1985, was strongly in favor of the class action suit (7). The Supreme Court went further than the trial court judge and invalidated the 1978 legislation. It stated very clearly that the state had breached its duty to preserve the corpus of the trust. The court stated, "It follows from our conclusion that the redesignation legislation is invalid, that the trust must be reconstituted to match as nearly as possible the holdings which comprised the trust when the 1978 law became effective." This statement, along with other provisions in the law, affords the mental health constituency an enforceable and far-reaching decision that should force the state to recognize and honor its obligations as a trustee of these lands. The income from the lands should be sufficient to provide the mental health program with a surplus of funds for the foreseeable future.

DISCUSSION

The Alaska mental health land suit may have special significance for other states. Although the information developed for the Alaska land trust lawsuit revealed the presence of mental health land grants in other states, this information is far from complete. Many states, not just western states, may have received land grants for insane asylums, charitable purposes, etc. Apparently, some of these land grants are at least partially intact. Interested parties should seek to identify these lands and determine for themselves whether the grants are being appropriately managed to support the programs they endow.

Alaska's management of the land trust, the lawsuit, and the context in which this whole process unfolded has been most instructive. It is clear that the legislature and the office of the governor, across several administrations, worked together to establish and implement a policy which was intended to avoid having any state land in public trust status. They were well acquainted with the legal issues and knew at the time that the 1978 law was probably unconstitutional (Alaska Attorney General Opinion, Feb. 8, 1982). It appears that they gambled on the weakness of the mental health constituency and hoped that their "redesignation and disposal" of the mental health trust lands would not be challenged.

They nearly succeeded because the mental health constituency in Alaska, as in most states, is not well organized, well financed, or united. Mental health services were a popular and strongly supported issue in 1956. In 1964 nearly 150 citizens were involved in developing the first state mental health plan. Many of these same citizens still reside in Alaska and have positions of leadership, but virtually none of them were involved in this latest struggle. Their lack of involvement raises some interesting questions. Was it

the result of changing interests, a willingness to rely on the government to fulfill its obligations, or perhaps a lack of understanding of the issue?

The mental health lands seem to have been an issue of such magnitude that neither the legislature nor the office of the governor was willing to address it independently. In discussions with individual legislators it became apparent that it was a troublesome problem which offered no political benefits. Apparently it was politically advantageous to have the issue decided by the judiciary.

It is not a simple matter to sue a state government. It was, in fact, a difficult step for a group of loosely associated citizens. Alaska is a small state, and the people being sued were often personal friends of those who brought the action. Maintaining a sufficient level of cohesion within the various groups involved was difficult, even impossible, at times. Funding was a major problem.

In spite of this lawsuit and its successful outcome, the future management of the mental health lands remains unclear. In view of the state's past performance, some reliable form of citizen oversight and involvement seems essential. Since the federal law does

not require citizen oversight, this can only be achieved through new legislative action or as a stipulation in the court settlement.

Assuming that the fundamental trust issue has been decided, the focus of attention can be expected to shift to defining a "mental health program" and determining the "necessary" level of funding. Will programs serving the alcoholic and the developmentally disabled, which have successfully achieved a separate identity, now return to the mental health umbrella? These and other questions will be the center of a new debate in Alaska.

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7. State of Alaska v Vern T Weiss et al, File S-653/678 (Alaska Supreme Ct, Number 2987, Oct 4, 1985)

Deceased Members of the American Psychiatric Association

The deaths of these members were reported to APA between Aug. 13 and Oct. 7, 1986.

Manfred I. Behrens, M.D.
Harold A. Bergner, M.D.
Howard Jerome Blechman, M.D.
Cornelis Boelhouwer, M.D.
G. Colket Caner, M.D.
George S. Cattanach, M.D.
Marion Chapman, M.D.
Ewin S. Chappell, M.D.
William B. Cline III, M.D.
Hermes Q. Cuervo, M.D.
Richard L. Daniel, M.D.
C. Douglas Darling, M.D.
Milton H. Firestone, M.D.
John W. Gaines, Jr., M.D.
Leonard Goldfarb, M.D.

Edward D. Greenwood, M.D.
Gertrude M. Gross, M.D.
Dorothy Harpham, M.D.
Peter B. Henderson, M.D.
Edgar B. Hodge, M.D.
Paul F. Hoefler, M.D.
Portia Hume, M.D.
Wolodymyr Iwanowycz, M.D.
Rose D. Jenkins, M.D.
George A. Jarvis, M.D.
Melvin M. Kayce, M.D.
Maria Kovacs-Szuts, M.D.
Rudolf Lampel, M.D.
James D. Mahoney, M.D.

Edward C. Mann, M.D.
J.T. May, M.D.
J. McClelland, Jr., M.D.
Aaron H. Meister, M.D.
Daniel G. Melvin, M.D.
Fernando M. Monserrate, M.D.
John Lincoln Moore, M.D.
R. Nysewander, M.D.
Alexander P. Orfirer, M.D.
Richard W. Reschke, M.D.
Leonard Rothschild, M.D.
Dayrel D. Smith, M.D.
Emile G. Stoloff, M.D.
Robert James Winters, D.O.

Book Forum

Nancy C. Andreason, M.D., Ph.D., Editor

PSYCHOANALYSIS

The Analysis of Defense: The Ego and the Mechanisms of Defense Revisited, by Joseph Sandler with Anna Freud. New York, International Universities Press, 1985, 556 pp., \$40.00.

One of the intriguing facts of psychoanalytic scholarship is that Anna Freud's short monograph *The Ego and the Mechanisms of Defense* (1), given to her father in 1935 for his 80th birthday, should remain the best book we have on the subject. *The Analysis of Defense* consists of a series of interviews with Anna Freud conducted by Joseph Sandler, Freud Professor of Psychoanalysis at the University of London. The interviews took place at the Hampstead Clinic during the years 1972 and 1973, when Anna Freud was 76 years old, and consisted of an almost page-by-page discussion of *The Ego and the Mechanisms of Defense*. During the interviews staff members of the clinic and visitors got to kibitz, but throughout the star was Miss Freud. These interviews, published piecemeal in the *Bulletin of the Hampstead Clinic*, are now brought together in this well-edited monograph.

Until the 1920s it was thought to be "unpsychoanalytic" to study adjustment to the external world. As Anna Freud reminisces to Sandler, "I remember Helena Deutsch, who was at that time in America, saying that I would finish myself with analysts forever with that book because I dealt with the ego and not with the id." Nevertheless, early on in her 1936 monograph Miss Freud stated, "The proper field for our observation is always the ego" (1, p. 6), and since 1936 analysts have chosen to follow her, not to ostracize her.

Although in his earliest papers on psychoanalysis Anna Freud's father had lucidly defined several defenses: the differential diagnosis and cataloging of the defense mechanisms eluded him. Most psychoanalytic writers since Sigmund Freud, in trying to examine defenses under higher and higher magnifications, have obfuscated them, for, like studying an impressionist painting, looking at defenses too closely makes them disappear in meaningless detail and complexity. One reason why *The Ego and the Mechanisms of Defense* has remained a classic reference on the subject is Anna Freud's capacity for simplicity. Thus, she describes defenses to Sandler as follows: "If you look at them microscopically, they all merge into each other. You will find repression anywhere you look. . . . The point is, one should not look at them [defenses] microscopically, but macroscopically, as big and separate mechanisms, structures, events. . . . [Then] the problem of separating them theoretically becomes negligible. You have to take off your glasses to look at them, not put them on" (p. 176). Later, she reminisces about the 1930s: "We didn't use quite the same terms, but often we used simpler terms. I had a discussion with Dr. Greenson yesterday about the term 'narcissistic homeostasis.' Dr. Greenson asked me what it really meant, and I said that it meant the person is pleased with himself. Dr. Greenson said: 'Why don't people say that?'" (p. 530). As the Sandler-Freud

dialogue continues, Anna Freud occasionally apologizes for her "simplifying tendency," but no apology is needed.

Sandler's interviews also give Anna Freud a chance to correct her 1936 monograph. For example, she tells us that when she called repression the least normal or the most pathogenic of the defense mechanisms, "I shouldn't have said that" (p. 235). Anna Freud also acknowledges that her original monograph suffered in translation. "The English is not mine," she reminds Sandler, "because at the time the book was published I did not yet write in English." For example, she points out that what she meant by "repetition compulsion" was "urge to repeat" and that her meaning was closer to a child's striving to master a difficult task than to a repetition compulsion neurosis.

Throughout, Sandler's book benefits from Anna Freud's humor. For example, she suggests to him that "bossiness" is a hallmark of altruism and that a person becomes an altruist not out of the "goodness of his heart, but out of the badness of his heart." She tells Sandler a new anecdote about the little boy with the lion fantasy in *The Ego and the Mechanisms of Defense*. On one occasion, the boy pointed to Sigmund Freud as he walked through Anna's and Sigmund's joint waiting room and offhandedly remarked, "Also sort of a lion."

Sandler's book has one failing. In its 530-page discussion of Anna Freud's original 193 pages, this book is occasionally guilty of the failing of which John O'Hara allegedly accused Henry James—chewing more than it bites off. At times Sandler becomes the very model of an establishment psychoanalyst: profound but obscure, ideologically correct but wordy and an interviewer who must apologize for his "pedantry." But, in his defense, Sandler plays the role of the Socratic straight man. He lets Anna Freud's humor shine through and, at the same time, permits her to carry out her cherished aim: "I really wanted to show things very clearly."

The book will be invaluable not only to people interested in the development of our understanding of defense mechanisms but also to anyone interested in Anna Freud's life. The answers to Sandler's thoughtful questions remind us what an important book Anna Freud wrote half a century ago and what a witty, moral, and thoroughly marvelous woman Sigmund Freud's youngest daughter must have been.

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GEORGE E. VAILLANT, M.D.
Hanover, N.H.

Son and Father: Before and Beyond the Oedipus Complex, by Peter Blos. New York, Free Press (Macmillan), 1985, 180 pp., \$22.50.

In Joe Orton's play *What the Butler Saw* (1), Geraldine responds to a query as to whether she ever had a father: "Oh,

I'm sure I did. My mother was frugal in her habits, but she'd never economize unwisely." Peter Blos similarly encourages us to concede the relevance of fathers. After suggesting that psychoanalytic theory has been too "monolithic and confined" in codifying the father-son relationship, he offers a revisionist view of the Oedipus complex, centered around the male protagonists. Blos is critical of established analytic theory in giving a narrow function to oedipal fathers, concentrating on "the restraining and punishing father under whose threat of retaliation the little boy abandons his competitive strivings, as well as his patricidal and incestuous animus" (p. 10). Blos first draws attention to the dyadic, preoedipal relationship, when the bond is affiliative, nurturant, and precompetitive and the father, idealized as "good" and "powerful," acts as a facilitator of individuation. Blos then describes various processes in the transition of the triadic, oedipal relationship, when, optimally, relative deidealization of the father occurs with other shifts if the son is to focus on self, identity, and external object relationships.

Blos largely ignores the descriptive data provided by writers such as Lamb (2) and Parke (3), who detailed the development and distinctive features of paternal-child relationships; their data would broaden and complement Blos's analytic observations. Blos's writing style is lucid, apart from two stylistic limitations. The first, an occasional retreat into metaphorical obfuscation and purple prose (e.g., a proposal that the re-engulfing mother drives the boy's "passionate turn to the father as savior" [p. 88]), reminds us that bathos is an ever-present risk for the analytic theorist. Second, Blos at times uses a proselyter's language and arguments, claiming "verification" on the basis of personal clinical observation. The degree to which observation of severely disturbed individuals allows hypotheses about normal development is not an unusual concern about analytic theorizing.

In offering interpretive insights about deviations in optimal development (e.g., when deidealization of the father does not occur), Blos dissects and clarifies with intellectual rigor. His commentaries on Shakespeare's Hamlet and Kafka's filial relationships are brilliant, detailing issues such as enmeshment and polarities between paternal benevolence and malevolence as well as the assumed pathological sequelae of indecisiveness, helplessness, procrastination, depression, and a sense of abandonment and annihilation.

Blos formulates a pathological process that is largely gender-specific, distinguishing contributions by fathers and mothers. Without denying that "mothers" and "fathers" (whatever their sex) show functional differences in parenting, I am not persuaded that Blos always describes gender-specific pathogenic parenting. Kafka's father could well be Portnoy's mother in the autobiographical note, suggesting that there may be malignant styles or components of parenting which, by their nature and irrespective of the sex of the parent, influence the child's self-esteem, identity, motivation, capacity for individuation, and later intimate relationships. Unfortunately, such general issues tend to be largely neglected by analytic theorists; Blos's revisionist view is no exception.

This book should join *On Adolescence* (4), Blos's earlier work, as a classic reference in adolescent psychiatry, and there will be few readers who will not appreciate Blos's keen intelligence, scholarship, and interpretive abilities.

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GORDON PARKER, M.D., PH.D., F.R.A.N.Z.C.P.
 Sydney, Australia

Freud for Historians, by Peter Gay. New York, Oxford University Press, 1985, 254 pp., \$17.95.

Psychoanalysis is three things: a system of psychiatry that organizes facts and theories about human behavior, a method of inquiry that generates data in that system, and a method of psychotherapeutic treatment. The origins of these three themes are inextricably intertwined, and for most psychoanalysts each of the three only makes sense when it is related to the other two. However, from its earliest years some psychoanalysts have been interested in "applied" psychoanalysis, the use of psychoanalytic psychology and, at times, even some aspects of the psychoanalytic method to enhance our understanding in areas far removed from clinical treatment. Art, literature, law, politics, cultural anthropology, biography, and history have all been the "patients" and, at times, perhaps the victims of applied psychoanalysis. Freud started it, with his comments on Oedipus and Hamlet and his studies of Leonardo, Michelangelo, Dostoevsky, "Totem and Taboo" (1), "The Future of an Illusion" (2), "Moses and Monotheism" (3), "Civilization and Its Discontents" (4), and others. Most psychoanalysts have been wary, fearful that their instrument, removed from its natural setting, would lose its precision and elegance at best and, at worst, would turn into a weapon. Peter Gay quotes from an unpublished letter of Freud, "In my opinion, psychoanalysis should never be used as a weapon in literary or political polemics" (p. 140). Gay adds that even Freud fell short of this ideal. He concludes, "It is certainly undeniable that the record Freudian historians, beginning with Freud himself, have compiled is less than confidence-inspiring" (p. 182). Most of the fields to which psychoanalysis has been applied are even more dissatisfied with the results. I remember more than a decade ago I was teaching a course on psychology and history with a distinguished historian. We each began by proudly announcing that we were not psychohistorians. It was clear that our credibility in our primary disciplines would be, if anything, enhanced.

Peter Gay is Sterling Professor of History at Yale University and a graduate of the Western New England Institute for Psychoanalysis. His central academic interest has been the application of psychoanalytic principles to historical inquiry. He has written more than a dozen books, and the current volume was published while he was in the midst of a trilogy on *The Bourgeois Experience, Victoria to Freud*. (Two volumes of this trilogy have been published so far [5, 6].) As both a distinguished historian and a trained psychoanalyst, he illustrates the principle that interdisciplinary scholarship really works only when a single scholar is well versed in both disciplines.

Freud for Historians is not what the title seems to suggest. It is not an introduction to psychoanalysis for those who wish to apply it to the study of history or for anyone else. It is, rather, a review of the troubled relationship between psychoanalysis and history. In fact, it is itself a history (although not a psychohistory—Gay has relatively little interest in a psychoanalytic understanding of the prejudices

and biases he describes so well or of the historians whose dread of psychology he criticizes). His basic argument is simple, and most of the brief text is occupied with examples rather than analyses of the issues. Gay's thesis is that "all history is in some measure psychohistory," although he adds that "psychohistory cannot be all of history" (p. x). He does, however, give psychology a privileged position: "Among all his auxiliary sciences, psychology is the historian's acknowledged principal aide" (p. 6). Further, he argues that psychoanalysis is, from the perspective of the historian, the psychology of choice. He begins the history of psychohistory with Erikson's biography of Luther in the 1950s and traces its rather stormy course since that time.

In summary, Gay tells us that historians have frequently attacked psychoanalysis with strong passions and little understanding, they have occasionally used its concepts with unimpressive results, but, again, with little understanding, and there have been a few brilliant examples of the potential yield when the disciplines are truly wed. In most of his examples it is only the first characteristic of psychoanalysis, that of a theory in psychology, which is applied, but in several of the most promising examples there is also some use of psychoanalysis as a method of inquiry. It may be that applied psychoanalysis is most successful when the coherence of its ideas and methods can be maintained in the process of its application. Gay does not discuss this issue, but if it turns out to be true, it would make psychoanalysis similar to the other academic disciplines that have been exploited by historians.

Gay is an enthusiastic advocate of his thesis; he wants historians to become more interested in and sophisticated in their use of psychoanalytic assistance. However, he is aware of some problems with his argument, and a psychoanalyst reader will detect others. He discusses, and dismisses, the most obvious one, that history is a bad patient because the method requires living and responding patients. However, the task for psychohistory is not to treat or cure but, rather, to enrich our understanding, and psychology is not to be the method but, rather, one of the ancillary tools.

A second, more difficult problem is whether psychoanalysis is the best psychology for historians. Gay formulates the question and asserts his conviction that it is, but skeptics will not be converted. Gay argues that psychoanalysis has long been interested in the tensions between the individual and society, the person and the culture, and the particularity of the self and the generality of the species, exactly the features of a psychology that should appeal to historians. He finds particularly attractive the psychoanalytic principle of multiple function, that one act can simultaneously have many purposes and many meanings (although he confounds it with and mislabels it as the earlier and less appealing concept of overdetermination, with its unscientific implication of more than total determinism). He believes that history needs a "general" psychology, and, following Hartmann, he argues that psychoanalysis is just that, even claiming that Freud "aimed from the beginning at a general psychology."

Here I would take issue with his reading of the historical record. Freud did believe that the demarcation between normal and pathological in psychology was artificial and not helpful, but a general psychology must do more than be relevant to the normal as well as the disordered. It must also encompass behavior not best understood in terms of conflict as well as capacities, developments, and defects that may shape the individual's subjective world but cannot be understood simply by exploring that world. The expansion of psychoanalytic thinking to embrace these issues was Hart-

mann's program, not Freud's, and most modern psychoanalysts believe that it was an error. However, if psychoanalysis is not a general psychology, and if historians do need one, then they may need more than just psychoanalysis. In addition, they will need some guidelines to pick and choose among the various psychologies.

Here Gay offers little assistance. This is no surprise, since psychologists and behavioral scientists have not settled the matter among themselves. But, of course, that is the problem. If psychologists cannot agree, how can a historian know what to do? One solution, rejected by Gay, is to admit to history those principles of psychoanalysis, or any other school of psychology, which become part of the general culture. One does not have to study psychoanalysis to think in terms of concepts such as conflict, repression, oedipal dynamics, or unconscious fears. However, as Gay correctly points out, one does have to learn psychoanalysis to use these concepts carefully, correctly, and to best advantage. Another solution, probably the best at present, is to recognize that history needs psychology and that it would be best to have the most powerful and comprehensive psychology available. At present, that means not one but several different approaches and, probably, like modern psychology itself, a pluralistic rather than an eclectic approach. Some historians should follow Gay's lead and master psychoanalysis; others should learn other schools of psychology. Their success in applying these methods should enrich psychoanalysis and psychology as well as history.

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ROBERT MICHELS, M.D.
New York, N.Y.

Presentations of Gender, by Robert Stoller, M.D. New Haven, Yale University Press, 1985, 213 pp., \$20.00.

This is Professor Stoller's sixth book, what he calls "another chapter in my ongoing search to understand the origins, development, dynamics, and pathology of gender identity" (p. vii). The book has two main goals: 1) to present Stoller's current thinking on gender identity and 2) to provide a "preliminary sketch of how a psychoanalyst can set up hypotheses and check them" (p. vii). Although the book draws on ideas previously published in four papers and five book chapters, it goes beyond a mere repetition of those works.

This book provides a rare glimpse into Professor Stoller's rancor, irony, frustrations, and struggle with the *furor theoreticus* of psychodynamic thinkers who substitute fancy rhetoric for true understanding in their attempt to understand the formation of gender identity. It is Stoller's impression that many clinical researchers of gender identity have misused and abused psychiatric nosology and have mishandled the clinical material related to gender identity disorders.

In effect, they have presented us with nothing more than other versions of the emperor's new clothes. In contrast, Stoller argues for a naturalistic, observational approach in psychoanalysis. To this end he presents a list of "idiosyncratic suggestions," which he hopes may serve as a guide for future researchers in gender identity disorders. Although one may take issue with Stoller's reluctance to employ a more traditional method in his inquiry (at times he sounds almost antiscience), his arguments often make sense. In the final analysis, he has an uncanny knack for getting to a truth and making it appear that his way may be better, even though you may disagree with him.

The very title of the book, *Presentations of Gender*, underscores a major problem one encounters in pursuing Stoller's method (that is, how to handle the vast scope of inquiry that his naturalistic observation of gender identity disorders encompasses). For Stoller, the clinical observer is immersed in an extraordinary field of observation that is boundless and quite ambiguous. Although he limits his book to male gender presentations, his range of material includes chapters on marked femininity in boys, biological influences on gender identity, degrees of boyhood femininity, child fetishism, origins of male transvestism, sex change surgery, and cross-cultural approaches to gender role and identity—including discussions of American Indians and the Sambia, a tribal society in New Guinea.

The first part of the book focuses on Stoller's ideas regarding the psychodynamics of gender identity disorders—specifically, the precursors of male transsexualism (essentially, his ideas have not changed since the 1960s). He then goes on to summarize his position on a variety of gender presentations (e.g., male primary and secondary transsexuals, female transsexuals, fetishistic cross-dressers, cross-gender homosexuals, intersexuals, hermaphrodites, psychotics, and casual cross-gender behavior). In the opening chapters he reviews his previous findings and reminds the reader that his original ideas on transsexualism were based on a rare group of patients who were primary transsexuals. He emphasizes this because it has been a sore point between Stoller and his critics. Professor Stoller feels misunderstood (and admits that he might have contributed to the misunderstanding) and wishes to set the record straight. His main point is that he has found a group of patients for whom trauma and conflict did not play a dominant role in the etiology of their transsexualism. It is his contention that psychoanalysis ought to accept the idea that some forms of behavior have nontraumatic origins.

What makes this book a gem is Stoller's excellent use of audiotaped clinical material, his candor in critically appraising his own hypotheses, and his focus on child gender disorders (a focus that takes up nearly half the book). The case of Mac (a child fetishist) is particularly well presented. Although Stoller refuses to generalize from a single case of fetishism to a model for fetishism, his hypotheses about the nature and treatment of fetishism (the condensing of one's "problems and their solutions in one efficient, ever-ready, exciting, gratifying act") are noteworthy. He sees a synergy of trauma, excessive and focal identification, and separation anxiety as being critical elements in the construction of a fetish (an object that "stands as a bridge between the infant's wanting to stay merged with the mother and to become an independent person"). In effect, while denying that he will generalize from a single case of fetishism, Stoller does just that. "Early boyhood fetishism," he concludes, "is the consequence of a constellation of events, not a single event" originating during the preoedipal phase of development. In

this sense he goes beyond Bak and Stewart (1) and Fenichel (2), who saw fetishism as primarily an oedipal configuration related to castration anxiety, denial of differences between the sexes, and the use of defensive denial.

Stoller warns us that as we read his book we may sometimes reach conclusions different from his interpretations. After all, he has committed himself to the notion that all psychoanalytic clinical reports should start with the phrase "once upon a time." In this sense, he is in agreement with Gregory Bateson (3), who recognized that the ability to tell a story was an essential aspect of human knowing, one that distinguished human intelligence from artificial intelligence. I thoroughly recommend this book to all students of gender identity disorders. Professor Stoller has taken part of his life's work and condensed it into a wonderful story, and for this he has earned our gratitude.

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LESLIE M. LOTHSTEIN, PH.D.
Cleveland, Ohio

SUBSTANCE ABUSE

Substance Abuse and Psychopathology, edited by Arthur I. Alterman. New York, Plenum, 1985, 394 pp., \$42.50.

In the 3 weeks between the arrival of the request to review this book and the arrival of the book itself, the following events occurred at the 334-bed psychiatric facility where I work:

A 48-year-old opiate-dependent health professional was admitted after a serious suicide attempt.

A patient on the alcoholism unit reported that her roommate, a 23-year-old alcohol and cocaine abuser, was secretly self-inducing vomiting after each meal.

A 27-year-old patient was transferred to the hospital from a free-standing alcoholism rehabilitation facility in a frank manic state.

A young man recovering from a recurrent schizophrenic psychosis returned from his first home visit with exacerbated symptoms. It was later found that he had smoked marijuana and had brought back a supply, which he shared with other patients.

A manic-depressive physician, an outpatient, celebrated his first year free of both alcohol and psychosis.

These everyday experiences are typical examples of the interface between substance abuse and psychopathology, yet the literature on this subject is both modest in volume and surprisingly difficult to access. Thus, Alterman's volume is a welcome addition.

The book is made up of an introductory overview and 12 chapters, each by different authors, loosely organized into two sections. The first covers substance abuse in different populations (the general population, psychiatric patients, those with affective disorders, and those with sociopathy). This section also contains a fascinating summary by McLel-

lan, Childress, and Woody of their studies relating drug of choice to psychopathology. Another chapter, by Castellani, Petrie, and Ellenwood, reviews current knowledge of the neurobiological mechanisms of drug-induced psychosis.

The second section concentrates, for the most part, on practical clinical problems. Included are chapter on the interactions between drugs of abuse and prescription drugs, the handling of substance abuse problems in an emergency room, neuropsychological findings in patients who abuse substances, family issues in substance abuse, and treatment of patients with two or more diagnoses.

Like other books made up of separate contributions of different authors, this book is not easy to read. The chapters vary widely in style and format, from reviews of the scientific literature, to presentations of the author's own work to the description of a treatment program illustrated by clinical vignettes. The reason for this uneven presentation may lie as much in the nature of the subject itself as in the editor's choices. The provision of a summary section at the conclusion of each chapter is helpful.

Substance Abuse and Psychopathology contains a great deal of information of use to psychiatrists. Clinicians in other disciplines may consider some of the chapters too technical but will nevertheless profit from much directly applicable material that is hard to find elsewhere.

Although the need for a coherent and comprehensive textbook in this area remains, Alterman has made a useful contribution and an important first step.

SHEILA BLUME, M.D.
Sayville, N.Y.

Recent Developments in Alcoholism, vol. 3, edited by Marc Galanter. New York, Plenum, 1985, 323 pp., \$45.00

Alcoholism research is a multidisciplinary area of investigation linking psychiatry, internal medicine, psychology, sociology, and basic sciences in an effort to decrease the morbidity and mortality of this illness. This volume is the third in an ongoing series sponsored by the American Medical Society on Alcoholism and the Research Society on Alcoholism. As in the two previous volumes, this volume includes four alcoholism research topics. The topics are grouped into sections that begin with an overview written by an expert in the area, followed by three to eight chapters detailing recent research findings. The topics covered here include high-risk studies, prostaglandins and leukotenes, cardiovascular effects, and cerebral functioning in social drinkers.

Psychiatric research has been most active in the first topic, high-risk studies. In this section, introduced by Donald Goodwin, M.D., various researchers detail current methods of evaluating children and young adults whose parents are alcoholic. The goal of these studies has been to find markers that might identify the 30% to 25% of offspring of alcoholics who will develop alcoholism. Strategies that appear promising include EEG and evoked-potential studies, monitoring behavioral responses to alcohol challenge, neuropsychological testing, and evaluation of familial and developmental patterns. Studies to date have focused on comparing children of alcoholics and children without a family history of alcoholism. This section reports on findings in these areas and comments on the need for follow-up of high-risk children with potential marker abnormalities to validate the findings.

The prostaglandin research section recognizes the limited biochemical knowledge of most readers interested in alcoholism. The overview provides an excellent introduction to the discovery, biochemistry, physiology, and pathophysiology of prostaglandins, and the following chapters detail the effects of alcohol on the synthesis and metabolism of prostaglandins as well as the interaction of alcohol with brain prostaglandins. Alcohol appears to increase CNS prostaglandin production; the hypothesis that this increase may be linked to some of the behavioral effects of alcohol warrants further investigation.

The final two sections of the volume deal with interesting questions about the effects of alcohol on social drinkers. Epidemiologic findings of low cardiac and total mortality in mild to moderate drinkers (1 to 2 drinks daily) has prompted attention in the lay press and the scientific community. Somewhat lost in the proclamations of this benefit of social drinking has been the well-known fact of high total mortality in heavy drinkers. Additionally, studies have not answered the question of whether encouraging nondrinkers to drink reduces their mortality. Some data suggest that nondrinkers are more likely to have family histories of alcoholism than social drinkers and therefore may be more likely to develop heavy drinking patterns. The section of the book on cardiovascular effects of alcohol reviews the epidemiologic evidence for low cardiac mortality in social drinkers. This discussion is balanced with chapters covering the links between alcohol consumption, hypertension, and cardiomyopathy.

The concluding section focuses on cognitive function and CAT scans in social drinkers. The research on cognitive functioning is far from definitive as to whether detrimental cognitive effects are limited to consumption of alcohol in quantities above a threshold or whether a continuum of damage exists. Evidence for both hypotheses is presented here along with discussion of statistical and methodologic difficulties in this area of research.

A book with "Recent Developments" in its title must be evaluated for the timeliness and importance of covered topics. References for the various chapters include journal citations through 1983. This seems quite current in view of the 1985 publishing date. The topics covered continue to be of research importance and will be for many years. This volume is highly recommended, especially for young researchers interested in alcoholism.

WILLIAM R. YATES, M.D.
Iowa City, Iowa

Alcohol and Substance Abuse in Adolescence, edited by Barry Stimmel. New York, Haworth Press, 1985, 206 pp., \$22.55.

This slender volume is the latest in the *Advances in Alcohol and Substance Abuse* series. As is the practice for this series, it is an edited collection of papers on a theme chosen on the basis of importance and timeliness. The subject of drug use among young people is certainly timely and important. However, with a rapidly changing subject at the very convergence of biomedical, sociological, and psychological disciplines, producing a multiauthor collection would seem to be an invitation to chaos. The title, *Alcohol and Substance Abuse in Adolescence*, alone should be enough to induce fatigue in a potential reader.

I am pleased to report that the editor has avoided the

pitfalls inherent in such an undertaking and produced a book that is useful, readable, and still faithful to its title. The volume is introduced by an orienting editorial and ended by a selective guide to reference sources in the field. Between are seven papers by different authors addressing separate topics in areas of their expertise. Each of these is a scholarly, readable presentation of either reviews of work in the area or data from current studies. Although the papers are drawn from different groups, they are selected well enough to be complementary in content and consistent enough in approach to provide a sense of unity and completeness.

The papers are an engaging mix of data and speculation, theory and method. In the section on the epidemiology of alcohol and drug abuse among adolescents we find reviews of several of the best epidemiologic surveys. The evidence seems to support the claim of a "drug epidemic" among adolescents in the mid-1960s to the mid-1970s, starting with marijuana and ending with cocaine "bringing up the tail of the epidemic." There is reason to believe the phenomenon may have reached a ceiling; encouraging evidence indicates a decrease in intensity of use among users. Likewise, there seems to have been a peak in the rise in alcohol use, although such use has settled at an alarmingly high level.

One of the papers presents an extensive longitudinal sociometric study comparing parental and peer influences on the adolescent. This study found that parental influence was predominant in determining educational goals, while peer influences were the predominant factor in initiation of drug use. Parental influences, however, seemed to be of greater importance in the transition from marijuana use to more extensive use of other illicit drugs.

Another paper reports an unusually intensive case study of sizable samples of nonpatient drug abusers drawn from noninstitutional sources in the community. The authors were able to study individuals who were not seeking treatment, not in trouble, and not decompensated but clearly regular users of excessive amounts of the various drugs of abuse. They observed an interesting hierarchy of adjustment involving sedative/hypnotic, opiate, amphetamine, and cocaine users and nonusers.

This collection of papers does not exhaustively cover the subject of adolescent substance abuse; treatment, for example, is not addressed at all. The book is, however, an excellent sampler designed to introduce the sophisticated neophyte to the state of the art in the field. Since the viewpoint and style are for the most part those of social psychology, it avoids the dryness of rigorous analysis of sociological data and does not require the enormous investment of faith demanded by a psychoanalytic approach. It should be a good read for behavioral scientists and clinicians.

DEMMIE MAYFIELD, M.D.
Kansas City, Mo.

MEDICAL ETHICS

The Breaking of Bodies and Minds: Torture, Psychiatric Abuse, and the Health Professions, edited by Eric Stover and Elena O. Nightingale, M.D. New York, W. H. Freeman and Co., 1985, 309 pp., \$21.95; \$11.95 (paper).

That torture was sanctioned as early as the time of the Roman Empire, that it was not cast from the legal system until Napoleon did so in 1808, and that it is still practiced regularly today in nearly one-third of the world's nations

should be enough to give pause to any rational, sensitive being. Of concern here is how even compassionate health professionals participate in stripping men and women of their humanity. A physician's primary responsibility can all too often be conveniently forgotten or uneasily ignored if clear ethical guidelines are not available for guidance and support. *The Breaking of Bodies and Minds* draws attention to the unfortunately not uncommon problem of what happens when one begins to serve the state instead of the citizen.

The product of a 1981 symposium on medical ethics and torture sponsored by the Committee on Scientific Freedom and Responsibility of the American Association for the Advancement of Science, this book brings together a variety of articles written not only by psychiatrists and other physicians but also by political scientists, journalists, and human rights workers. Editors Stover and Nightingale provide a historical context in their introduction, stating their aim to "explore both how repressive governments have enlisted the aid of medical practitioners in suppressing dissent and what steps need to be taken to prevent such professional complicity, and ultimately, to end the abuses themselves" (p. 3). Issues regularly raised throughout the text are those ethical and moral dilemmas confronted by health professionals who engage in ill-treatment and the effects of this ill-treatment on the victim and society.

Overall, the quality of the writing is high—fully documented and readable prose marked by clarity and passion. The essays have been well integrated, so the text flows smoothly and logically. Although there is some overlap in coverage, in the main this constitutes reinforcement rather than repetition. Perhaps what is most important—and most frightening—about the book is the effect it has in making one aware of how pervasive and serious this issue is. In "Torture and the Ethics of Medicine," Albert R. Jonsen and Leonard A. Sagan point out that some "forty years after Nuremberg . . . torture with no pretense of research has become, in many countries, a common instrument of government" (p. 31).

Part one, *Torture*, investigates how medical personnel unwittingly participate in ill-treatment through resuscitating victims and evaluating their condition and through lending legitimacy simply through their presence. The moral dilemmas faced, especially by military or prison physicians, who may be asked to perform duties consistent with their professional responsibilities such as caring for a tortured person, are also explored. "Physical and Psychiatric Effects of Torture: Two Medical Studies" presents the medical and psychological long-term aftereffects of torture. The authors of this chapter address the need for sufficient data to establish a specific torture syndrome, distinct from posttraumatic stress syndrome, in order to develop appropriate treatment protocols. The call for ethical codes and for action to combat abuses is sounded consistently throughout this section. Although some may say that the issue of torture is political in nature and therefore outside the realm of proper professional concern, the different authors repeatedly make it clear that, insofar as politics affects the quality of life, political torture is an appropriately pertinent and compelling issue.

Part two, *Psychiatric Abuse*, focuses primarily on abuses in the Soviet Union and describes what measures have been taken to end them. A recurrent theme is that of psychiatry's vulnerability to being co-opted by the state because of the psychiatrist's role in protecting the populace from dangerous or potentially dangerous individuals. "Psychiatrists and Dissenters in the Soviet Union" provides a history of psychiatric abuse in that country and discusses how schizophrenia became an umbrella term used to justify incarceration.

Walter Reich's "The World of Soviet Psychiatry" picks up this thread and spins the tale of how leading Soviet psychiatrist Dr. Andrei V. Snezhnevsky developed the concept of this psychosis. Snezhnevsky's claim to have discovered clinical principles that allow any schizophrenic patient to be assigned to one of three categories of schizophrenia—each having a distinct genetic basis, quickly assumed primary import and influence in Soviet psychiatry. Reich speculates, probably correctly, that in many cases psychiatrists in the Soviet Union are not making unprofessional diagnoses for political reasons but truly believe that the "strange" behavior of dissenters establishes that they are mentally ill. The nature of Snezhnevsky's diagnostic system then allows this strangeness to be called schizophrenia. One of the most interesting chapters is Reich's case study of General Grigorenko, a Soviet dissident and defector who was diagnosed as mentally ill and committed to hospitals for the criminally insane in the Soviet Union. After conducting a full-scale psychiatric examination, Reich's American team concluded that Grigorenko did not suffer from a diagnosable mental illness. Reich hopes their findings will occasion reflection on the social functions of psychiatry, its special vulnerabilities, and its relationship to diagnosis and the law. Provocative is his concluding statement: "Where the [the Soviet psychiatrists] claimed obsession, we found perseverance; where they cited delusion, we found rationality; where they identified psychotic recklessness, we found committed devotion; and where they diagnosed pathology, we found health" (p. 20-). Such variance should serve as a reminder of the influence society has on psychiatric judgments, as well as a reminder of the influence psychiatric judgments have on social norms.

In examining the role of health professionals in one of man's most heinous crimes—that of willful destruction of another—*The Breaching of Bodies and Minds* paradoxically reminds us of our humanity and of our responsibility to it.

LISA M. SCHWERTZ, Ph.D.
Florence, Ala.

Culture and Self: Asian and Western Perspectives, edited by Anthony J. Marsella, George DeVos, and Francis L.K. Hsu. New York, Tavistock (Methuen), 1985, 307 pp., \$27.00; \$12.95 (paper).

This volume is intended to explain the revival of interest in the self in Western and Asian thought. If this task seems insurmountable, it can be fully appreciated only through a study of the previous writings of the editors, who are highly regarded scholars of Asian studies. Their earlier writings confirm the total familiarity of these men with their chosen specialty. It is surprising, however, to read about the awakening of the self in Japan, because we know that in Japan a heightened awareness of self, i.e., self-centeredness, represents an offense to society and family. When self-centredness becomes an irreversible trait, it is likely to be viewed as a symptom of severe neurosis, i.e., *shinkeitsu*, which requires psychiatric treatment.

Perhaps there is also less of a revival of the self in Confucian thought, as we learn from Tu Wei-ming's essay "Selfhood and Otherness in Confucian Thought." Professor Tu of Harvard University is one of the leading Confucian scholars of recent decades. In an earlier publication Tu Wei-ming defined Confucian selfhood as regarding the self as the center of relationships and as a dynamic process of spiritual development. Quite apart from his discussion of

selfhood, Tu's chapter is a striking addition to this book, as Tu Wei-ming's analyses of Confucian writings have long been the outstanding elucidations of the thought of this sage.

Long before the self occupied any importance in Asian reasoning, the accentuation of the self was a Western phenomenon. It played a considerable role at the beginning of this century in the works of outstanding thinkers such as William James, G.H. Mead, Carl Gustav Jung, and several others who "elevated the Self to a position of primacy in their theories." When their emphasis on the self decreased in the 1930s, it was continued in the theories of psychoanalysis and phenomenology.

It is therefore all the more surprising to be confronted with the self in Western and Asian thought. Only by studying previous writings of Anthony J. Marsella, George DeVos, Francis L.K. Hsu, and the other contributors to this book, all of whom have long been familiar with the subject and are highly regarded in the field of Asian studies, can the dimension of this endeavor be fully appreciated.

Culture and Self will be an important book for the student of the Orient—philosopher, anthropologist, or psychologist—and it should receive the acclaim it deserves. For me, it was a great pleasure to read.

ILZA VEITH, Ph.D., DR.MED.SC.
San Francisco, Calif.

AFFECTIVE DISORDERS

Depression in Multidisciplinary Perspective, edited by Alfred Dean. New York, Brunner/Mazel, 1985, 272 pp., \$27.50.

The concept of a multidisciplinary perspective on a topic is a commendable one. However, different disciplines often work within parochial definitions. Therefore, asking three disciplines to give their perspectives on a topic like depression is more likely to produce three informative contributions on three different topics than three views of a single topic. Not surprisingly, this book is at times commendable, confusing, and informative; ultimately it is disappointing.

The book is separated into three sections: Psychosocial Epidemiology and Etiology, Special Diagnostic and Treatment Issues and Neglected Areas, and Therapeutic Innovations. Not surprisingly, the first section includes detailed reports of a number of epidemiological studies of depression. However, the meaning given to the term "depression" by the epidemiologists is quite different from that used by the authors in the section on special diagnostic and treatment issues. This is perhaps best illustrated if one compares the chapter on depressive symptoms in early adolescence in section one with the chapter on selected issues in the study of childhood depression in section two. Quite clearly, the first chapter surveys depressive symptoms and the second is a clear discussion of a depressive syndrome. Taken together, they may create the illusion of an interdisciplinary "exchange" of views on this topic, but in reality the authors are not talking about the same topic at all.

This fundamental problem notwithstanding, there are several excellent chapters in this book that deserve specific comment, notably Dr. Dean's own contribution on the epidemiology of depression, which is a scholarly and critical review of the subject. Dr. Akiskal cogently presents his concept of chronic depression and makes a compelling argument for the reconsideration of the diagnosis of "characterological depression." Dr. Friedman's chapter on

diagnosis and treatment of depression in the elderly is also quite complete, but it includes some inaccurate treatment recommendations, such as his belief that desmethylimipramine is the antidepressant of choice in the treatment of the elderly because it does not cause orthostatic hypotension. This is, unfortunately, not the case, and it has been shown that desmethylimipramine produces orthostatic hypotension equivalent to that of imipramine (1). Furthermore, one would appreciate more caution from Dr. Friedman with respect to his "excitement" over trazodone as a treatment in elderly patients with depression. What unexpected problems trazodone will produce are not fully known, but certainly priapism has turned out to be a more frequent and dangerous side effect than originally anticipated. Finally, Dr. Friedman's reluctance to use monoamine oxidase inhibitors (MAOIs) in an elderly population should be weighed against the study of Georgotas et al. (2), which demonstrated that elderly patients with depression can have a good therapeutic response when given phenelzine and that it is a reasonably safe treatment.

Dr. Davidson's chapter on patients who do not respond to tricyclic antidepressants accurately chronicles the clinically well-worn, albeit unproven regimens for treating such patients. However, a substantial problem in this chapter is, again, the discussion of the new antidepressants. Dr. Davidson contends that some of these drugs may be effective when standard treatments have failed and that, in general, the new drugs have fewer side effects. Both statements are somewhat misleading. First of all, there are no well-designed controlled studies demonstrating that any of the new antidepressants work when a therapeutic level of a standard tricyclic has failed (3). Second, the new generation of antidepressants may indeed not have the same side effects as tricyclics, but that is not to say that they have fewer side effects, only different ones. The seizures induced by bupropion and the hemolytic anemia and drug fever caused by nomifensine are but two examples of this.

Dr. Gorman's contribution reflects the right spirit in her title, "*Possible Laboratory Tests in Depression*" (my italics). She emphasizes the crucial differentiation between the longstanding use of 3-methoxy-4-hydroxyphenylglycol (MHPG) measurements as a research technique and the fact that MHPG measurements are not clinically useful at this time. She then presents an excellent critique demonstrating why the dexamethasone suppression test (DST) is not a useful diagnostic tool. Unfortunately, I think Dr. Gorman groups measurements of tricyclic antidepressant plasma concentrations with other "lab tests," thus underplaying the usefulness of these measurements in routine clinical practice (3).

Finally, Drs. Becker and Hineberg readily admit that they intended "to provide an uncritical review" of cognitive behavioral treatments of depression. They are more than truthful.

Dr. Dean has taken care to ensure a high quality of style and scholarship and consequently has produced a book that includes a number of well-written, informative chapters on interesting and important topics. However, the number of books of this breed is huge, and many of them contain the same type of chapters by the same authors. This book does not distinguish itself from the others and in that sense is disappointing.

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STEVEN P. ROOSE, M.D.
New York, N.Y.

Definition of Suicide, by Edwin Shneidman. New York, John Wiley & Sons, 1985, 247 pp., \$22.95.

In this book, Dr. Shneidman's intent was "to write a fairly slim book about an admittedly heavy subject" (p. v). Although this is not an empirical book, it is filled with the clinical wisdom of an experienced clinician who has devoted his professional life to understanding the vicissitudes of suicidal behavior. In a unique way, Dr. Shneidman draws on the writings of several key mentors and scholars to integrate perspectives on suicide. These writings are Stephen Pepper's *World Hypotheses* (1), James G. Miller's *Living Systems* (2), Henry A. Murray's *Explorations in Personality* (3), and Herman Melville's *Moby Dick*. Shneidman's goal was to provide "fresh notes about what suicide is and, concomitantly, to imply realistic and practical measures for preventing suicide" (p. v).

Shneidman's main premise is that "effective remediation depends on accurate assessment which, in turn, depends on meaningful definition. Prevention rests on assessment; assessment rests on definition" (p. vi). Thus, he notes that defining 10 common characteristics of suicide is his "principal contribution to suicidology to date" (p. vi). Shneidman clearly states these characteristics and discusses their importance. They are the common internal attitude toward suicide and the common stimulus, stressor, purpose, goal, emotion, cognitive state, interpersonal act, action, and consistency in suicide. Shneidman carefully qualifies his presentation of the common features of suicide by stating, "Each suicide is an idiosyncratic event. In suicide, overall, there are no universals, absolutes, or 'alls'" (p. 121). Furthermore, he points out that he is talking specifically about suicide, making a distinction between the characteristics of individuals who commit suicide and those of people who exhibit nonfatal suicidal behavior.

Having described the common characteristics of suicide, Shneidman presents his definition of suicide, which, he asserts, concerns "how . . . acts of suicide should be understood and how they should be regarded, especially by the academic and professional communities" (p. 3). His proposed definition is, "Currently in the Western world, suicide is a conscious act of self-induced annihilation, best understood as a multidimensional malaise in a needful individual who defines an issue for which the suicide is perceived as the best solution" (p. 203).

Derived from this definition are implications for suicide prevention. For example, because there are multiple facets to suicide, Shneidman proposes that treatment of a suicidal person must incorporate approaches that address the biological, sociological, developmental, philosophical, and cognitive aspects of an individual's functioning. Thus, the treatment of a suicidal individual should be carried out by more than one therapist; Shneidman advocates a "therapeutic council." Furthermore, treatment involves very practical approaches that address the frustrated needs of the suicidal

person. Shneidman specifically describes how he carries out such a treatment process. In this way, he hopes to achieve the most basic ingredient of suicide prevention—public education about suicidal behavior. His commitment to this is evident in his conclusion, "In the last analysis, the prevention of suicide is everybody's business" (p. 238).

I have attempted to highlight salient features of *Definition of Suicide*. Ed Shneidman's ideas are very thought provoking and in many ways controversial, but they are based on a genuine commitment to understand, to update theory and clinical practice, to clarify, and to stimulate dialogue. This book therefore should be read by all who are seriously concerned about suicide prevention.

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CYNTHIA R. PFEFFER, M.D.
White Plains, N.Y.

PAIN

The Chronic Pain Patient: Evaluation and Management, by Philip L. Goldenberg, M.D., Ph.D., and Richard A. DePaul, M.D. Basel, S. Karger, 1985; 140 pp., \$37.75.

This small book is well written and has several important messages. The authors, a neurosurgeon and a psychiatrist, are qualified authorities in this area who rely on their experience at the Chronic Pain Clinic of the University of Texas Medical School at Houston, where, over a period of 8 years, they evaluated and treated 1,000 patients. They report that the vast majority of their patients had significant improvement in ability to manage their pain, experienced marked lessening in their social disability, and improved in their personal functioning.

The book is well organized and proceeds from the examination of what constitutes pain to a definition of different types of pain: psychogenic pain (from noxious or destructive stimuli), pathological pain (from a faulty nervous system in which there is no noxious element or tissue destruction), and psychological pain (perceived pain connected with depression, conversion disorder, or other psychological states). The authors describe four classes of people experiencing chronic pain. "The patient who needs to suffer" has a history from childhood or early adulthood of many operations and many other physician contacts; for this patient there is a temporal relationship between stressful life events and physical suffering. "The overwhelmed patient" has a classic operant conditioning complex in which sickness and disability are

their own reward; this patient "enjoys" the sick role and the associated privileges of being cared for and excused from responsibility. In "the psychogenic patient" the perception of pain is primarily due to depression, unresolved grief, a delusional system that is part of a psychosis, anxiety, or what the authors call "hysterical neurosis." Most interesting of all and most neglected is "the assigned patient," who is made "chronic" by his or her physicians. This usually occurs after an accident in which acute pain is treated by analgesics that are continued, usually because the physician does not adequately inquire concerning the diminution of pain or the change in the character of pain. The patient becomes progressively more dependent on analgesics and has the view that he or she has chronic pain.

The authors outline a comprehensive evaluation, starting with taking a history that examines in considerable detail the patient's health, interpersonal relationships, family, and childhood as well as the setting and circumstances of the acute problem and its progression to chronicity. Significant relatives are interviewed, and the patient is given a physical examination. At the end of this evaluation the physician comes to a conclusion concerning the particular kind of pain the patient is experiencing and directs the treatment accordingly. The authors repeat that analgesics are to be used only for acute pain and cannot control situations of chronic pain. In their concluding chapter the authors state, in italics, "Beware of pain medications!" and "There is no analgesic for chronic pain!"—essentially the themes of their book.

As to management, the patient must work with the physician in moving toward a rehabilitation process in which analgesics are stopped (with the exception of the terminal cancer patient) and there is a reexamination and redefinition of the immediate purpose. Most patients treated for chronic pain expect to receive a better analgesic. In most instances what is experienced as pain is discomfort connected with withdrawal from analgesics. Patients find that they need their medicine to relieve what they believe and what they have been encouraged to believe is pain. In the rehabilitation process the physician offers the patient a better understanding of the causes of what is experienced as pain and encourages the patient's willingness to let go of the sick role. The physician must be prepared to treat or refer for treatment patients suffering from anxiety, depression, regression, and psychosis. The patient may be helped by tranquilizers, antidepressants, relaxation techniques, support groups, transcutaneous stimulation, and biofeedback. Less commonly the physician may have to consider nerve blocks, hypnosis, or acupuncture.

This is a good book and is highly recommended for those who care for patients with chronic pain, especially primary care physicians and consultation-liaison psychiatrists. It may also be of interest to professionals who themselves have a problem in this area.

NORMAN B. LEVY, M.D.
Valhalla, N.Y.

Reprints of Book Forum reviews are not available.

Letters to the Editor

Yohimbine- and Tranylcypromine-Induced Postural Hypotension

SIR: We read with interest the letter "Yohimbine and Imipramine-Induced Orthostasia" by Mark Hyatt, M.D., and Michael Messer, M.D. (March 1986 issue), describing a patient with imipramine-induced orthostatic hypotension who was successfully treated with yohimbine. Recently we treated a depressed patient with tranylcypromine, and she experienced severe orthostatic hypotension. A trial of yohimbine was then attempted, but the result was disappointing.

Ms. A was a 24-year-old depressed woman with vegetative symptoms and suicidal ideation. We began by treating her with a tyramine-free diet and tranylcypromine, 10 mg b.i.d. orally. Within 3 days, she experienced symptomatic orthostatic hypotension, with decreases in systolic pressure averaging 30 mm Hg. On the fifth day of treatment, her monoamine oxidase level was 54% of the pretreatment level. Therapy with fludrocortisone, 0.1 mg q.i.d., was started. On the 12th treatment day, the fludrocortisone was stopped and yohimbine was started, at a dose of 5.4 mg b.i.d. Orthostatic symptoms continued, and the dose of yohimbine was increased on the 17th treatment day to 5.4 mg t.i.d. Ms. A continued to experience orthostatic symptoms, with decreases in systolic pressure of 30–50 mm Hg and in diastolic pressure of 40 mm Hg. On the 25th treatment day, we prescribed the use of pressure stockings, and the dose of yohimbine was increased to 5.4 mg q.i.d. There was no improvement, and on the 29th treatment day, we discontinued both the tranylcypromine and the yohimbine. The total length of treatment with yohimbine was 15 days, without significant benefit.

Orthostatic hypotension induced by antidepressants remains a therapeutic problem, and its mechanism continues to be elusive. Central stimulation of α_2 -adrenergic receptors, such as might occur with increased synaptic concentration of catecholamines from monoamine oxidase inhibitor (MAOI) therapy, could contribute to the hypotension, as proposed by Drs. Hyatt and Messer. Most tricyclic antidepressants (1) and monoamine oxidase inhibitors (unpublished data of S.C. Lin and E. Richelson) are weak antagonists of α_2 -adrenergic receptors; as such, they have a weak opposing effect on the postulated α_2 -receptor activation, and thus, apparently, orthostatic hypotension is observed. However, one exception, mianserin, has a relatively high affinity for human brain α_2 -adrenergic receptors (2). Theoretically, then, mianserin should produce significant central α_2 -blocking effects and minimize orthostatic hypotension. Unfortunately, this effect is not observed clinically (3). Unlike the tricyclic antidepressants, MAOIs probably have little direct central or peripheral adrenergic, histaminic, or muscarinic receptor activity (unpublished data of S.C. Lin and E. Richelson) to account for the orthostatic effect observed on the basis of receptor

blockade. The common end point of stimulation of central α_2 -adrenergic receptors by increased synaptic concentration of norepinephrine produced by tricyclic antidepressants and MAOIs seems to be a plausible mechanism to explain the orthostatic hypotension induced by both classes of drugs. However, our case report does not support this hypothesis because central α_2 antagonism by yohimbine did not correct the postural hypotension, at least not with tranylcypromine.

We agree with Drs. Hyatt and Messer that controlled studies are needed to examine further the role of yohimbine in the management of orthostatic hypotension produced by antidepressants.

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SIONG-CHI LIN, M.D.
TIMOTHY HSU, M.D.
PAUL A. FREDRICKSON, M.D.
ELLIOTT RICHELSON, M.D.
Rochester, Minn.

More on Ganser's Syndrome and DSM-III

SIR: In his letter to the Editor "Ganser Syndrome and DSM-III" (March 1986 issue), Ferdinand Knobloch, M.D., noted that Ganser's syndrome may be classified incorrectly in *DSM-III* as a prototypic factitious disorder with psychological symptoms. *DSM-III* notes that in this disorder the unconscious goal of symptom production is the assumption of the patient role. It is thought that severe personality disorder is present in the majority of cases. Individuals who have the disorder are described as either unusually suggestible or negativistic.

Dr. Knobloch describes a series of cases in which the unconscious "final goal" of the patient with the symptoms of Ganser's syndrome was not to assume the patient role per se but to avoid legal consequences; consistent with Ganser's initial description of the syndrome, Dr. Knobloch emphasized the presence of dissociative defenses in his cases.

We have recently reported two separate case studies of visually impaired, mentally retarded boys presenting with classic symptoms of Ganser's syndrome (1, 2). Both boys also had Tourette's syndrome. Our child patients' symptoms of Ganser's syndrome took the form of exaggerating the degree of their visual impairment, particularly in their educational environments. These boys alternated between being either pathologically compliant or pathologically negativistic.

tic. In addition, they exhibited classic examples of the syndrome of approximate answers. For example, in response to questioning, one patient answered that Ronald Reagan rode George Washington's horse, that a three-legged stool has four legs, and that a large dog has five legs while a small dog has only four. Neither of these boys appeared intent on assuming the patient role. It is unclear but doubtful whether they had some other "anal goal" in mind.

We have entertained two hypotheses (which are not incompatible) regarding the mediation of our patients' symptoms of Ganser's syndrome. First, because of their developmental disabilities, each of them had experienced a variety of operant conditioning situations. It is possible that consequent to difficulty in accurately discriminating stimuli and/or in generalizing required responses, they presented with seemingly factitious behavior. Such a perspective might also be applicable to the prisoners described by Dr. Knobloch. Another hypothesis relates to our patients' symptoms of Tourette's disorder. Each patient exhibited complex patterns of echolalia, palilalia, and echokinesis. We have conceptualized these specific symptoms of Tourette's disorder as being akin to pathological compliance (suggestibility) and on the other side of the same coin, pathological negativism. Many of the symptoms of Ganser's syndrome (including the syndrome of approximate answers) in our patients may represent complex examples of pathological compliance/negativism.

We agree with Dr. Knobloch's suggestion that the subsuming of all cases of Ganser's syndrome under the classification of factitious disorder with psychological symptoms may be reductionistic. If others have had similar findings in children, we would be interested in hearing about their cases.

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JACOB KERBESHIAN, M.D.
LARRY BURD, M.S.
Grand Forks, N. Dak.

Chronic Pain and Posttraumatic Stress Disorder

SIR: I am intrigued by the findings of Benedikt and Kolb in their article "Preliminary Findings on Chronic Pain and Posttraumatic Stress Disorder" (July 1986 issue) about the coexistence of chronic pain syndrome and posttraumatic stress disorder. Their experiences are similar to my own in treating a patient who had complaints of chronic pain, depression, and suicidal ideation.

Mr. A, a 35-year-old paraplegic patient who had made two previous suicide attempts and had had a course of ECT 4 months earlier, entered his fourth psychiatric hospitalization. Initially, Mr. A was angry, uncooperative, and suspicious; he had severe back pain, poverty of speech, nightmares, insomnia, and suicidal ideation. His medications included diazepam, 20-40 mg/day; perphenazine, 24 mg/day; diphenhydramine hydrochloride, 5 mg

prn; trazodone, 150 mg/day; benztropine mesylate, 2 mg every 4 hours as needed; phenoxylate hydrochloride with atropine sulfate (Lomotil), 2 capsules every 2 hours as needed; and oxycodone hydrochloride with acetaminophen (Percocet), 1-2 tablets every 2 hours as needed.

Mr. A previously had been given the diagnosis of chronic pain syndrome, alcohol abuse, borderline personality, and major depressive disorder. However, a carefully taken developmental history, confirmed by two independent sources, elicited no history of major social or psychological problems. At age 17 Mr. A, a good student and track star, had been a passenger in a car that flipped over, and he had sustained a spinal cord injury. He was taken to a small community hospital but initially was not evaluated for a spinal cord injury. Five days later he was transferred to a larger hospital, but because the neurosurgeon was ill, surgery was delayed for 4 months. Mr. A lost bowel and bladder control and most motor and sensory functioning in his legs. His hospital course was complicated by urinary tract infections and decubiti that required surgical intervention. Eventually Mr. A made a remarkable physical recovery and could walk short distances using canes. However, he was angry, isolated, had recurring nightmares and flashback experiences, was estranged from his family and friends, and was chronically unemployed.

During his most recent psychiatric hospitalization Mr. A's diagnoses were revised to posttraumatic stress disorder and chronic pain syndrome. His medications were modified to amitriptyline, 200 mg h.s., and acetaminophen with codeine (Tylenol No. 4) and Lomotil as needed. Dream, emotion, and sleep logs, in conjunction with supportive psychotherapy, were used to help him identify and work through his feelings about the accident and his injury. After discharge Mr. A continued in supportive therapy for 2 years. He reestablished relationships with his family and friends, got married, and found part-time employment.

This case and Kolb and Benedikt's findings demonstrate a possible link between problems with intractable chronic pain, substance abuse, affective instability, and posttraumatic stress disorder. In Mr. A's case, once the coexistence of posttraumatic stress disorder was acknowledged and therapeutic interventions were made to lessen his distress, his pain became more manageable, his affective instability resolved, and he was able to reintegrate into society.

MARK HYMAN RAPAPORT, M.D.
Bethesda, Md.

Obsessive-Compulsive Disorder and Borderline Personality Disorder

SIR: The article "Clinical Characteristics and Family History in DSM-III Obsessive-Compulsive Disorder" by Steven A. Rasmussen, M.D., and Ming T. Tsuang, M.D., Ph.D., (March 1986 issue) is a valuable contribution to the understanding of obsessive-compulsive disorder and is consistent with our own experience in dealing with obsessive-compulsive disorder patients. However, we were surprised at the total absence of any diagnosis of DSM-III axis II borderline personality disorder in their series of patients, as no less than 20% (8 of 39) of our patients with obsessive-compulsive disorder would fit such an axis II diagnosis. A possible explanation for the difference between the two populations may be that 9% of the patients in their report had a

concomitant histrionic personality disorder—a category that often overlaps with borderline or narcissistic personality disorder (1). It is noteworthy that our findings seem to be in accordance with Otto Kernberg's description (2) of frequent polysymptomatic neuroses (e.g., multiple phobias, obsessive-compulsive symptoms, and chronic, diffuse anxiety) in patients with a borderline personality organization.

Treatment trials for all of our eight borderline patients, who received either behavior therapy (response prevention) or pharmacotherapy (clomipramine), failed mostly because of very poor compliance. Eventually, we decided to exclude further borderline patients from our current treatment study of obsessive-compulsive disorder. Interestingly, that specific subgroup of patients has not been mentioned in previously reported treatment failures with obsessive-compulsive patients (3–5). If our observation is not due to a sample bias possibly linked to a local phenomenon, then it may have two clinical implications. First, conventional treatment of obsessive-compulsive disorder patients with borderline personality should be expected to encounter many difficulties, as we have mentioned. It may well be that these patients would respond more favorably to a different therapeutic approach of the dynamic-analytic type suggested for borderline patients (2). Second, further studies of treatment of obsessive-compulsive disorder should look more closely at the features common to patients who are excluded or who drop out. The fact that borderline patients presenting with obsessive-compulsive disorder tend to be excluded from therapy studies of obsessive-compulsive disorder may result in overly optimistic interpretation of the efficacy of treatment.

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HAGGAI HERMESH, M.D.
ANTON SHAHAR, PH.D.
HANAN MUNITZ, M.D., B.S.
Petah Tiqva, Israel

Drs. Rasmussen and Tsuang Reply

SIR: We agree with Dr. Hermesh and associates that the careful delineation of coexisting axis II personality disorders in obsessive-compulsive disorder has important prognostic and therapeutic implications. We have made an initial attempt to categorize DSM-III axis II disorders in probands with obsessive-compulsive disorder by using a semistructured interview adapted from the personality section of the *Structured Clinical Interview for DSM-III* (1). The difference in the prevalence of borderline personality disorder between the two groups is most likely due to differences in the index

populations, differences in operational criteria for making the diagnosis of borderline personality, or a combination of the two. The reliability and validity of DSM-III diagnostic criteria in the personality disorders continue to be controversial issues. Several authors have noted that DSM-III criteria for histrionic personality may define a disorder that is more similar to that of the borderline patient than to the more classic, traditional descriptions of hysterical personality (2, 3).

Since receiving the letter of Dr. Hermesh et al., we have taken the opportunity to carefully review the axis II diagnoses of our original 44 obsessive-compulsive disorder patients. All four patients (9% of the total sample) whose primary diagnosis was histrionic personality also exhibited some symptoms characteristic of borderline personality disorder. We also reviewed the axis II data for our total sample of 100 patients with obsessive-compulsive disorder and found that histrionic personality was present in 8% and borderline personality in 4%. We chose not to complicate the presentation of data in the original paper by giving multiple axis II diagnoses.

Dr. Hermesh et al. imply that their findings are supported by Dr. Kernberg's observations that there are frequent polysymptomatic neuroses among patients with borderline personality. However, to our knowledge no one has systematically studied the frequency of obsessive-compulsive symptoms in a well defined population of patients with a primary diagnosis of borderline personality disorder. Further doubt about the uniqueness of the correlation occurs on reading the Kernberg entry in the *Comprehensive Textbook of Psychiatry* cited by Hermesh and associates in their letter (their reference 2, p. 1084): "Although some borderline patients present remarkably few symptoms, most of them present the polysymptomatic neuroses described in the literature, including chronic, diffuse anxiety; multiple phobias; obsessive-compulsive symptoms; . . . dissociative reactions; hypochondriasis; paranoid trends; polymorphous perverse sexual trends; and the classical prepsychotic personality structures—namely, paranoid personality, schizoid personality, and hypomanic personality structures." In fact, with the exception of a small group of impulsive compulsive patients (4), the majority of our obsessive-compulsive patients fulfill none of the DSM-III criteria for the diagnosis of borderline personality disorder.

Finally, we totally agree with Dr. Hermesh et al.'s observation that these patients (whether one calls them borderline or oral hysteric) tend to respond poorly to both behavioral and psychopharmacologic treatment. This observation is also consistent with that of Rappaport and Yayura-Tobias (personal communication). A multicenter trial of clomipramine that is scheduled to begin shortly in the United States has listed various personality disorders as exclusion criteria. Like Dr. Hermesh and colleagues, we would like to emphasize the importance of collecting systematic phenomenologic, follow-up, and family data on an epidemiologically defined sample, as opposed to a sample that has been preselected by meeting criteria for a treatment study.

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STEVEN A. RASMUSSEN, M.D.
Providence, R.I.

MING T. TSUANG, M.D., Ph.D.
Brockton, Mass.

Hypofrontality in Schizophrenia as Assessed by PET

SIR: The report "Comparison of PET Measurement of Local Brain Glucose Metabolism and CAT Measurement of Brain Atrophy in Chronic Schizophrenia and Depression" by Arthur S. Kling, M.D., and associates (February 1986 issue) asserts that they failed to replicate the finding of diminished frontal lobe metabolic rate that has been reported in three earlier studies by other investigators. Their article oversimplifies several methodological issues and deserves comment.

Contrary to their claim in the précis of their article, Kling et al. did find relatively lower metabolic rates in the high frontal area of schizophrenic subjects (0.92) than of control subjects (0.97), and this they statistically confirmed ($t=3.5$, $p<.001$). This matches our report (1) of a similar finding in the right high frontal cortex of schizophrenic (1.09 and control (1.14) subjects ($t=1.7$, $p<.04$, one-tailed). Thus, their finding of hypofrontality actually exceeds ours in statistical strength and is hardly strong support for their claim in the abstract that "a previously reported metabolic 'hypofrontality' was not confirmed." The authors' application of methods of adjustment for number of comparisons is unjustified in replicating a significant finding in the three previous studies they cite. Such an adjustment would allow any group using positron emission tomography (PET) to disconfirm any and all findings by other groups merely by increasing the number of brain areas they test statistically. In addition, although Kling et al. found that a multivariate analysis failed to reach significance, their sample size (six schizophrenic patients) was only about one-third the size of ours (16 schizophrenic subjects), increasing the risk of type II error.

Kling et al. suggested that the regions of the frontal cortex which we used included portions of the lateral ventricles. Our data were obtained on a plane above the ventricles, and our anterior segment did not include them. Even on a plane passing through the midventricular level, the cortex still remains at least 2.2 cm thick with moderate dilation (grade 4 enlargement, Zatz's scale). Further, since Kling et al. found low metabolic rates in the frontal cortex, this argument does not seem entirely relevant.

Kling et al. omitted any experimental task that would control the pattern of brain metabolism in their study. They suggest that "an inherent weakness in using the FDG technique is the variability between patients with respect to cognitive activity and affective states during the procedure." As it was the cognitive and affective states that differed between the patients and the normal control subjects under study, it seems that PET's sensitivity is more of an inherent strength of the method. The weakness seems less inherent in PET than in the experimental design Kling and associates chose.

Finally, in an attempt to minimize the effects that uncontrolled medication of patients might have had on their results, Kling et al. reviewed the literature on PET studies of

the effects of neuroleptics and concluded that neuroleptics do not affect metabolic rate. The studies they cited do not provide direct experimental data on this issue. Two other published studies that they did not cite do, however. Wolkin et al. (2) found significant increases in the frontal cortex with neuroleptic treatment, as did DeLisi et al. (3) (although frontal/occipital ratios were not affected).

The great physiological sensitivity of PET raises even further the need for control of clinical, pharmacological, and behavioral variables; the small sample sizes employed necessitate our enhanced concern about type II as well as type I statistical errors.

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MONTE S. BUCHSBAUM, M.D.
JOSEPH C. WU, M.D.
Irvine, Calif.

Dr. Kling and Associates Reply

SIR: A claim for a significantly lower cerebral metabolic rate of glucose use in the high frontal regions of schizophrenic patients than in normal control subjects is not supported by data either from Buchsbaum et al. (reference 1 in the letter) or from our own report. In fact, Buchsbaum et al. presented in their table 2 surprisingly higher rates of glucose use for schizophrenic than for control subjects in all 12 sectors of the three cerebral slices chosen for analysis. There is also little indication that "at cortical levels below the primary areas, a pattern of relative hypofrontality and of relatively diminished AP [anteroposterior] gradients" could be observed; the schizophrenic subjects showed higher rates of glucose use in anterior than in posterior sectors in all three slices, and anteroposterior ratios (1.031) in supraventricular slices reflected neither diminished frontal metabolism nor significant deviation from that of control subjects (1.079), for which not even a marginal one-tailed t comparison ($t=1.48$, $df=33$, $p=.07$) gives support. This anteroposterior ratio reflects a high posterior metabolic rate but not a low anterior rate in schizophrenic subjects. Even if a regional hypometabolism is postulated before investigation (which may justify an unconservative one-tailed t comparison), it cannot be considered in isolation from the other regional comparisons.

A pattern similar to that shown by the data of Buchsbaum et al. was observed in our results (table 2 of our article, p. 178). Although regional comparisons indicated a lower cerebral metabolic rate of glucose use for right frontal, Broca, and Wernicke regions in uncorrected measures, the high intercorrelations between regions (1, 2) and the multiple t tests performed after nonsignificant analysis of variance required adjustment by the Bonferroni method simply to avoid finding one or more of these tests significant by chance. Thus, observed small differences may be sampling errors,

and the risk of a false-negative (beta) error has been more widely acceptable than the type I (false-positive) error from overzealous interpretation of a marginal difference.

It is not only remarkable that the schizophrenic group in Buchsbaum et al.'s 1984 report showed markedly higher rates of glucose use in all sectors than did controls, but the eight schizophrenic subjects in comparison with six control subjects in their 1982 report (3) had shown lower frontal sector ratios. However, the simultaneous comparison of four sectors in each slice does not permit interpreting only a single comparison as significant without adjustment. Buchsbaum and associates state in their letter that the adjustment for multiple comparisons is "unjustified." We disagree on the basis of our having used sound statistical methods when analyzing multiple comparisons (4). The sector difference ($t=2.49$, $df=12$, $p=.032$) would be nonsignificant if correctly considered in the three within-slice anterior comparisons ($p=.093$). If only a single interpretation is given, it is not clear which type of error in interpretation (type I or type II) is committed.

With respect to the argument that "neuroleptics do not affect metabolic rate," we stated on page 179 of our article that "the effects of neuroleptics on cerebral metabolic rate cannot be excluded as an explanation of some of the differences." Thus, we have left open the question of the influence of neuroleptics on cerebral glucose metabolism.

Our data are meant to strike a note of caution, without reproducing the risk of reporting a difference in results concerning schizophrenic patients' cerebral metabolism when there may not be one.

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ARTHUR S. KLING, M.D.
E. JEFFREY METTER, M.D.
WALTER H. RIEGE, PH.D.
DAVID E. KUHLE, M.D.
Sepulveda, Calif.

Libido in Women Receiving Trazodone

SIR: Nanette Gartrell, M.D., in the article "Increased Libido in Women Receiving Trazodone" (June 1986 issue), presented the cases of three depressed women whose libido increased to above premorbid levels during trazodone treatment. I have several questions concerning the report.

First, were these patients ever given a trial of any other antidepressant? If this had been done and no increased libido had occurred, the case for trazodone's uniqueness in this regard would have been bolstered.

Second, did these patients have any form of bipolar disorder? This possibility was suggested especially by the patient who "reestablished sexual relationships with three

former sexual partners (she had previously been sexually monogamous)." Was trazodone evoking hypomania?

Third, Dr. Gartrell's language fails to indicate the patients' sexual orientation. As we don't know what might be of interest to further research, why make characteristics of patients obscure? "Former sexual partners" should be identified as men or women.

KENNETH A. NAKDIMEN, M.D.
New York, N.Y.

SIR: We read with interest Dr. Gartrell's report that six of 13 women (46%) whom she treated with trazodone "experienced a substantial increase in libido coinciding with a remission of depressive or dysthymic symptoms."

We have treated a number of depressed women in our affective disorders clinic with trazodone without noticing increased libido beyond a return to predepression baseline. Of 23 depressed female outpatients currently taking trazodone, none has experienced an increase in libido beyond her predepression baseline level. The diagnoses of these patients are major depressive disorder with melancholia ($N=3$); major depressive disorder without melancholia ($N=18$), and dysthymic disorder ($N=2$). Most of these women are in the 35-50-year age range and take an average daily dose of 225 mg. Seventeen of the 23 take only trazodone, and the remainder take benzodiazepines as well.

Perhaps the dramatically increased libido experienced by Dr. Gartrell's patients represents part of a hypomanic episode induced by trazodone. It would be interesting to know whether any of these women have a personal or family history of bipolar disorder.

KENNETH JAFFE, M.D.
H. DOUGLAS BARNSHAW, M.D.
RITA WEINGOURT, M.N., C.S.
MARY E. KENNEDY, M.S.N., C.S.
Springfield, Mass.

Dr. Gartrell Replies

SIR: I appreciate the opportunity to respond to Dr. Nakdimen and Dr. Jaffe and associates.

None of the patients described in my report had any personal or family history of bipolar disorder. Likewise, none of these women demonstrated symptoms of hypomania during treatment with trazodone. The increased libido was experienced by both heterosexual and lesbian patients. No changes in sexual orientation occurred as a result of the trazodone.

NANETTE GARTRELL, M.D.
Boston, Mass.

More on Multiple Personality Disorder

SIR: Permit me to join in the controversy in your letter pages concerning the prevalence of multiple personality disorder. It seems to me that the original paper by Drs. Bliss and Jeppsen (1) did not so much seek to establish the prevalence of the disorder as to determine whether the diagnosis is often missed. In view of the history of childhood abuse in these cases and the fact that the disorder is treatable, any diagnostic lacuna in this field would be a grave injustice to the victims.

A cursory review of *DSM-III* and recent diagnostic population studies (2) suggests that simple screening for the disorder is not easily feasible. For instance, the Diagnostic Interview Schedule (3) does not even address dissociative disorders. The tables of kappa coefficients in appendix F of *DSM-III* suggest that in phase 1 of the field trials, just two patients with any kind of dissociative disorder were examined; the number dropped to one in the second phase. No children with dissociative disorder were found in the course of the field trials.

It is not uncommon for one therapist to diagnose multiple personality objectively, using very strict criteria, while another, using the same criteria, will not be able to diagnose the disorder in the same patient. Further, the diagnostic outcome might be reversed for the same two therapists with respect to another patient.

In a paper read at the First International Conference on Multiple Personality/Dissociative Disorders in 1984, I addressed this issue. The difficulty does not arise entirely from factors residing in the patient or the therapist. Rather, the diagnosis of multiple personality disorder (and, to a lesser extent, dissociative disorder in general) depends on the relationship between the patient and the therapist. I am not speaking here of the therapeutic alliance, although it is essential. Patients who have revealed their multiplicity to one therapist have disguised it with others, even though they may have liked a therapist and felt the therapy was of some use. On the other hand, patients have dropped out of treatment because they have felt threatened by the therapist's discovery of their multiplicity, even though a good alliance has been achieved.

The objective approach to diagnosis provided by *DSM-III* can confirm a diagnosis of multiple personality disorder; however, although a diagnostic interview can lead one to suspect the disorder, it cannot be used to make the diagnosis. People who have learned to hide their dissociations over a period of many years are not likely to give up their defenses just because the person facing them is a psychiatrist.

We need new diagnostic tools. Until we find a way of including the therapist-patient relationship in the diagnostic process, I do not believe the prevalence of multiple personality disorder or dissociative disorder in general can be established.

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OLIVER FRENCH, M.D.
Ithaca, N.Y.

SIR: Allow me to enter the dispute now under way about the authenticity of the recent exponential upsurge in the prevalence of multiple personality disorder, as exemplified by the exchange of letters in the December 1985 (1) and June 1986 (2) issues of the *Journal*. I have been in the practice of clinical psychiatry for the past 40 years. My practice has been primarily psychotherapeutic, but I have had my share of difficult patients. I have had hospital privileges and have used them. During this extended period, my experience with

multiple personality disorder has consisted of one very doubtful case. Interested by the spate of current reports, I have conducted a very informal poll of my colleagues. Uniformly, they report seeing no instances, or no more than one or two, of multiple personality disorder in their careers up to now.

How can this discrepancy be explained? I cannot accept that my colleagues and I have been so singularly lacking in diagnostic acumen as to miss recognizing an entity now being reported in the hundreds, even thousands. The suggestion that the pre-*DSM-III* criteria for the diagnosis of schizophrenia were so broad as to swallow up cases of multiple personality disorder is interesting but undocumented and could account only for a certain proportion of the current wave of cases of multiple personality disorder. It seems likely that we are witnessing another example of the tendency in the history of psychiatry for certain conditions (i.e. "shell shock," neurasthenia) to be recognized, rise in popularity, and then decline in accordance with largely cultural determinants. Iatrogenic influences operating on suggestible patients in the interests of secondary gain (for psychiatrists as well as patients) cannot be excluded as a possible reason for the discrepancy.

I have recently seen two cases of multiple personality disorder demonstrated on videotape by psychiatric residents at a local hospital. I felt that the factors I have just mentioned were operative, but I was also struck by the bolstering of defenses—with a stultifying effect on psychotherapeutic progress—exerted by concentration on the characteristics of the individual personalities rather than the patients' underlying conflicts.

In closing, I would like to repeat my question to Drs. Ludolph, Bliss, and Kluft: Why have my colleagues and I seen so few cases of multiple personality disorder?

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PAUL CHODOFF, M.D.
Washington, D.C.

Dr. Kluft Replies

SIR: In the course of his long and distinguished career, Dr. Chodoff has witnessed the rise of numerous ideas and enthusiasms in the field of psychiatry and observed their waxings and wanings as they gradually assume their rightful place (if any) within the science of our discipline. He suspects that the recent increase in the diagnosis, treatment, and scholarly study of multiple personality disorder may reflect cultural and iatrogenic influences rather than a breakthrough in our understanding of this complex and chronic dissociative pathology. Opinions, however eloquent, are not scientific data and cannot be represented as such. Either to assume that the new findings on multiple personality disorder are immune to the influences that commonly surround new areas of knowledge or to "discount them in advance" would be unfortunate. Dr. Chodoff asks, If multiple personality disorder is not rare, why have he and his colleagues seen so few cases? In stressing the possibility of the first type of error, he appears to minimize the risks of the second.

I am among a growing number of investigators whose

convergent findings suggest that multiple personality disorder is not rare. In the last 13 years I have interviewed more than 250 individuals with multiple personality disorder, initially diagnosed by over 150 colleagues. Only five were sent or presented by trainees. Since 1981 I have codirected a course on multiple personality disorder at each annual meeting of the American Psychiatric Association. Of the several hundred psychiatrists who have attended, the vast majority had already encountered patients with multiple personality disorder. With a small number of egregious exceptions, both the colleagues who sent me patients and those who attended the courses were thoughtful and extremely circumspect.

In disagreement with Dr. Chodoff, I find the evidence convincing that patients with multiple personality disorder have long been misdiagnosed. The average patient acquires 3.6 erroneous diagnoses during 6.8 years spent within the mental health system between a first evaluation for symptoms referable to multiple personality disorder and an accurate diagnosis (1). For example, half of the patients in the Putnam et al. series (1) had previous diagnoses of schizophrenia. The gratifying response of patients diagnosed as having multiple personality disorder to treatment for this disorder (2) strongly suggests that the schizophrenic diagnoses were in error.

Multiple personality disorder is most parsimoniously understood as a posttraumatic dissociative disorder of childhood onset, associated in 97% of cases with overwhelming and abusive experiences (1). Coons and Milstein (3) documented patients' reports of sexual abuse in 85% of their series, indicating that the accounts of traumas given by patients with multiple personality disorder should not be dismissed as mere fantasy.

Multiple personality disorder is usually misdiagnosed because our knowledge of the condition remains rudimentary, and the findings most relevant to its diagnosis have been published quite recently. Many of these observations suggest the need to revise many longstanding beliefs about multiple personality disorder (4). Woodruff and associates (5) pointed out that a disease is a cluster of symptoms and/or signs with a more or less predictable course. We now understand that the expectation that multiple personality disorder will present itself openly and be played up for secondary gain is misleading; this constitutes an uncommon presentation (4). Usually its core phenomena are covert and/or dissimulated: one sees a polysymptomatic picture suggestive of several types of physical and emotional disorders, in the context of which the features of multiple personality disorder are embedded (1, 3, 4). I have interviewed patients with multiple personality disorder for over a decade to learn about the natural history of the disorder. Most of the patients devoted considerable effort to disguising and denying their condition (4). While 6% were quite exhibitionistic, 94% were not. Once the patient is diagnosed as having multiple personality disorder and the prior homeostasis of the dissociative defenses is disturbed, the pathology is more clearly evident. Also, unfortunately, it is characteristic of any therapist new to multiple personality disorder to become transiently fascinated with the phenomenology before settling down to the hard work of the therapy. These two factors often lead to a regrettable tendency to commit the "post hoc, ergo propter hoc" fallacy and infer that iatrogenesis has occurred. Dr. Chodoff's letter is a caution to the profession against the errors attendant upon countertransferenceal fascination. My letter speaks to the risks attendant upon countertransferenceal skepticism.

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RICHARD P. KLUFT, M.D.
Philadelphia, Pa.

Overdiagnosis of Depression in the Medically Ill

SIR: In the article "Depression in the Medically Ill: An Overview" (June 1986 issue), Gary Rodin, M.D., and Karen Voshart, B.Sc., thoughtfully discuss reasons for the underdiagnosis of depression in patients with physical illness. They correctly point out that depressive symptoms and depressive syndromes are frequently missed by treating physicians, who may either dismiss them altogether or attribute them to the medical illness itself. Consequently, undiagnosed and untreated depressive syndromes can result in noncompliance with treatment regimens, neglect of self-care, and even suicidal behavior.

Whereas this problem of underdiagnosis by nonpsychiatric physicians has been well documented and well summarized by Rodin and Voshart, we have found that psychiatry residents on a consultation-liaison rotation often *overdiagnose* depression (1). In our experience, different syndromes can be overdiagnosed in the following ways.

1. A major depressive episode is overdiagnosed not only because the physical illness itself causes neurovegetative changes but also because the expected sick role (2) is confused with depressive behavior (e.g., regression, social withdrawal, relinquishment of responsibility).

2. Organic affective disorder is overdiagnosed because the resident presumes that the presence of a physical illness (e.g., pancreatic carcinoma, myocardial infarction) warrants the diagnosis even in the absence of a documented pathophysiological mechanism affecting the central nervous system.

3. Adjustment disorder with depressed mood is overdiagnosed because the possibility of an independent major depression or dysthymia is not considered, because bias leads to labeling certain illness behavior as maladaptive when it deviates from the resident's personal or sociocultural standards, and because depression is confused with normal grief, in which self-esteem is not impaired despite the loss of limb or bodily function (1).

As Rodin and Voshart point out, the underdiagnosis of depression in the medically ill may result in failure to treat a disorder that not only causes psychological distress but also may increase the likelihood of suicide or impede compliance with medical treatment and ultimate recovery or rehabilitation. However, the overdiagnosis of depression has risks as well. These risks include alienation from patients and staff on medical services due to overemphasis on psychopathology, and unnecessary or overly burdensome treatment, including

injudicious prescription of antidepressant medication. Rodin and Voshart touch on this idea when they comment that depressive symptoms do not always reflect a depressive syndrome, but we would like to have seen more emphasis on the other side of this most difficult diagnostic issue.

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SAMUEL W. PERRY, M.D.
DAVID F. CELLA, PH.D.
New York, N.Y.

Dr. Rodin and Ms. Voshart Reply

SIR: We are grateful to Drs. Perry and Cella for their favorable comments regarding our review article on depression in the medically ill and for their warning that phenomenological approaches may lead to neglect of psychosocial factors. We similarly emphasized in an earlier publication (1) the importance of psychotherapeutic approaches to the medically ill. Nevertheless, it seems justifiable to give greater weight to underdiagnosis than to overdiagnosis of major depression in this population for the following reasons.

1. Although depressive symptoms have been reported in up to one-third of medical patients, referral rates to psychiatry in general hospitals may be less than 3% (2). In the primary care setting, less than 10% of psychiatric disorders may be noted by attending nonpsychiatric physicians (3). Thus, even if psychiatrists overdiagnose major depression, the majority of medical patients with this condition are probably not referred for psychiatric assessment.

2. Depressive symptoms in the medically ill are often presumed to be "understandable" and inevitable and therefore unresponsive to treatment. Unfortunately, when there is an evident psychological basis for depressive symptoms, physicians may assume that investigation or treatment is not indicated (4).

3. The value of somatic symptoms in the diagnosis of depression in the medically ill may have been underestimated in the past. The diagnostic specificity of such symptoms for depression depends, in fact, upon the nature of the specific medical illness. For example, we found in a study of dialysis patients (5) that although fatigue, insomnia, and loss of libido were common in the entire sample, anorexia and weight loss distinguished those with the diagnosis of major depression.

We agree that the diagnostic category of organic affective disorder is troublesome. Since the specific pathophysiological mechanisms of most depressions have not been substantiated and since it is likely that most depressions are multifactorial

in origin, a unicausal etiological diagnosis is difficult to support. Similarly, the presumption that an adjustment disorder represents a reaction to a particular event may overlook other precipitating factors or mistakenly ascribe causation to a coincidental occurrence. We also concur that psychiatric diagnoses, including that of major depression, should be made judiciously and that the experience of illness should be addressed whether or not a particular psychiatric diagnosis has been made. On the other hand, diagnostic labeling is not always deleterious to the patient. Diagnoses sometimes lead not only to specific therapeutic interventions but also to more constructive attitudes toward medical patients. For example, ward staff may be less irritated with uncooperative patients when their noncompliant behavior is seen to be due to a depressive disorder rather than to willful refusal.

In conclusion, we support the plea of Drs. Perry and Cella for psychiatrists to be attuned to the human dilemma of medically ill patients but suggest that this need not preclude a thorough diagnostic assessment. Indeed, integration of empathic understanding with the scientific method should remain a central task for psychiatry and the rest of medicine.

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GARY RODIN, M.D.
KAREN VOSHART, B.Sc.
Toronto, Ont., Canada

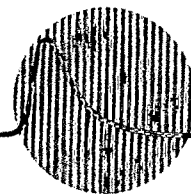
Corrections

On the cover and in the table of contents of the November 1986 issue, the first name of one of the authors of "Lethal Catastrophe" by Mann, Caroff, Bleier, et al. was misspelled. The correct name is Stephan C. Mann. The staff regrets this error.

The author of the book review of *Blood Brothers: Siblings as Writers* (pages 1615-1616 of the December 1986 issue) has informed us that there is an error in the review. He stated that Anthony and Peter Shaffer were the "one instance where both brothers are still alive and writing." There is in fact another that has just come to his attention, Lawrence and Gerald Durrell.

Reprints of Letters to the Editor are not available.

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Anterograde amnesia and paradoxical reactions have been reported with HALCION and some other benzodiazepines.

PRECAUTIONS: *General:* In elderly and/or debilitated patients, treatment should be initiated at 0.125 mg to decrease the possibility of development of oversedation, dizziness or impaired coordination. Caution should be exercised in patients with signs or symptoms of depression which could be intensified by hypnotic drugs. Suicidal tendencies and intentional overdosage is more common in these patients. The usual precautions should be observed in patients with impaired renal or hepatic function and chronic pulmonary insufficiency. *Information for Patients:* Alert patients about: (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing prescribed dosage, (e) possible worsening of sleep after discontinuing HALCION. *Laboratory Tests:* Not ordinarily required in otherwise healthy patients. *Drug Interactions:* Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistaminics, ethanol, and other CNS depressants. Pharmacokinetic interactions of benzodiazepines with other drugs have been reported, e.g., coadministration with either cimetidine or erythromycin reduced clearance, prolonged elimination half-life, and approximately doubled plasma levels of triazolam, hence increased clinical observation and consideration of dosage reduction may be appropriate. *Carcinogenesis, Mutagenesis, Impairment of Fertility:* No evidence of carcinogenic potential was observed in mice during a 24-month study with HALCION in doses up to 4000 times the human dose. *Pregnancy:* Benzodiazepines may cause fetal damage if administered during pregnancy. The child born of a mother who is on benzodiazepines may be at some risk for withdrawal symptoms and neonatal flaccidity during the postnatal period. *Nursing Mothers:* Administration to nursing mothers is not recommended. *Pediatric Use:* Safety and efficacy in children below the age of 18 have not been established.

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Drowsiness	14.0	6.4
Headache	9.7	8.4
Dizziness	7.8	3.1
Nervousness	5.2	4.5
Lightheadedness	4.9	0.9
Coordination Disorder/Ataxia	4.6	0.8
Gastrointestinal		
Nausea/Vomiting	4.6	3.7

In addition, the following adverse events have been reported less frequently (i.e., 0.9-0.5%): euphoria, tachycardia, tiredness, confusional states/memory impairment, cramps/pain, depression, visual disturbances.

Rare (i.e., less than 0.5%) adverse reactions included constipation, taste alterations, diarrhea, dry mouth, dermatitis/eczema, drowsiness, dreaming/nightmares, insomnia, paresthesia, tinnitus, dysphagia, weakness, congestion, death from hepatic failure in a patient also receiving diuretic drugs.

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WARNINGS: Tardive Dyskinesia: This syndrome (potentially irreversible, involuntary, dysrhythmic movements) may develop in patients treated with neuroleptic (antipsychotic) drugs. Fevers appear highest among the elderly, especially women; it is impossible to predict which patients are likely to develop the syndrome. Both rise of syndrome development and likelihood of becoming irreversible are believed to increase with duration of treatment and total cumulative dose; the syndrome can develop after brief treatment periods at low doses. There is no known treatment. partial or complete remission may occur if neuroleptic treatment is withdrawn. Neuroleptic treatment may suppress or partially suppress signs and symptoms of the syndrome and thereby mask the underlying disease process. Effect of symptomatic suppression upon long-term course of the syndrome is unknown. Prescribe neuroleptic treatment for patients suffering from a chronic illness that is known to respond to neuroleptic drugs and for whom alternative treatments are not available or appropriate. In those requiring chronic treatment the smallest dose and shortest duration of treatment producing satisfactory clinical response should be sought. Need for treatment should be reassessed periodically. Consider discontinuing treatment if signs and symptoms of tardive dyskinesia appear; some patients may require treatment despite presence of the syndrome.

Usage in Pregnancy: Studies in pregnant patients have not been carried out. Animal reproductive studies have not demonstrated teratogenic potential. Anticipated benefits must be weighed against the unknown risks to the fetus if used in pregnant patients.

Nursing Mothers: Data are not available on the content of MOBAN in the milk of nursing mothers.

Usage in Children: Use of MOBAN in children below the age of twelve years is not recommended because safe and effective conditions for its usage have not been established. MOBAN has not been shown effective in the management of behavioral complications in patients with mental retardation.

Sulfites Sensitivity: MOBAN concentrate contains sodium metabisulfite, a sulfite that may cause allergic-type reactions (e.g., hives, itching, wheezing, anaphylaxis) in certain susceptible persons. Although the overall prevalence of sulfite sensitivity in the general population is probably low, it is seen more frequently in asthmatics or in atopic nonasthmatic persons.

PRECAUTIONS: Some patients may note drowsiness initially; advise against activities requiring mental alertness until response to the drug has been established. Increased activity has been noted in patients receiving MOBAN. Caution should be exercised where increased activity may be harmful. MOBAN does not lower the seizure threshold in experimental animals to the degree needed with more sedating antipsychotic drugs; in humans convulsive seizures have been reported in a few instances. This tablet preparation contains calcium metabisulfite as an excipient; calcium ions may interfere with the absorption of preparations containing phenytoin sodium and tetracyclines. MOBAN has an emetogenic effect in animals. A similar effect may occur in humans and may obscure signs of intestinal obstruction or brain tumor. Neuroleptic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent in vitro, a factor of potential importance if the presence of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time.

ADVERSE REACTIONS: CNS EFFECTS: Most frequently occurring effect is initial drowsiness that generally subsides with continued usage or lowering of the dose. Noted less frequently were depression, hyperactivity and euphoria.

Neurological—Extrapyramidal Reactions: Noted below may occur in susceptible individuals, usually reversible with appropriate management.

Akathisia: Motor restlessness may occur early.

Parkinson Syndrome: Akinesia, characterized by rigidity, immobility and reduction of voluntary movements and tremor, have been observed. Occurrence is less frequent than akathisia.

Dystonic Syndrome: Prolonged abnormal contractions of muscle groups occur infrequently. Symptoms may be managed by the addition of a synthetic antiparkinson agent (other than L-Dopa), small doses of sedative drugs, and/or reduction in dosage.

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Autonomic Nervous System: Occasional blurring of vision, tachycardia, nausea, dry mouth and salivation. Urinary retention and constipation may occur, particularly if anticholinergic drugs are used to treat extrapyramidal symptoms.

Laboratory Tests: Rare report of leucopenia and leucocytosis; treatment with MOBAN may continue if clinical symptoms are absent. Alterations of blood glucose, liver function tests, BUN, and red blood cells have not been considered clinically significant.

Metabolic and Endocrine Effects: Alteration of thyroid function has not been significant. Amenorrhea has been reported infrequently. Resumption of menses in previously amenorrheic women has been reported. Initial heavy menses may occur. Galactorrhea and gynecomastia have been reported infrequently. Increase in libido has been noted in some patients. Impotence has not been reported. Although both weight gain and weight loss have been in the direction of normal or ideal weight, excessive weight gain has not occurred with MOBAN.

Hepatic Effects: There have been rare reports of clinically significant alterations in liver function in association with MOBAN use.

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INDICATIONS: ASENDIN is indicated for relief of symptoms of depression in patients with neurotic or reactive depressive disorders as well as endogenous and psychotic depressions and depression accompanied by anxiety or agitation.

CONTRAINDICATIONS: Prior hypersensitivity to dibenzoxazine compounds and in the acute recovery phase following myocardial infarction. Do not give concomitantly with monoamine oxidase inhibitors. Hypertensive crises, severe convulsions, and deaths have occurred in patients receiving tricyclic antidepressants and monoamine oxidase inhibitors simultaneously. Before replacing a monoamine oxidase inhibitor with ASENDIN® amoxapine, allow a minimum of 14 days to elapse, then initiate cautiously, with gradual increase in dosage until optimum response is achieved.

WARNINGS: Tardive Dyskinesia: Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may develop in patients treated with neuroleptic (ie, antipsychotic) drugs. (Amoxapine is not an antipsychotic, but it has substantive neuroleptic activity.) Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of neuroleptic treatment, which patients are likely to develop the syndrome. Whether neuroleptic drug products differ in their potential to cause tardive dyskinesia is unknown.

Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dosage of neuroleptic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods of low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if neuroleptic treatment is withdrawn. Neuroleptic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying disease process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, neuroleptics should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic neuroleptic treatment should generally be reserved for patients who suffer from a chronic illness that (1) is known to respond to neuroleptic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on neuroleptics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome. (For further information about the description of tardive dyskinesia and its clinical detection, please refer to the sections on Information for Patients and Adverse Reactions.)

Use with caution in patients with history of urinary retention, angle-closure glaucoma, or increased intraocular pressure. Watch patients with cardiovascular disorders closely. Tricyclic antidepressants, particularly in high doses, can induce sinus tachycardia, changes in conduction time, and arrhythmias. Myocardial infarction and stroke have been reported with drugs of this class. Take extreme caution in patients with history of convulsive disorders or those with overt or latent seizure disorders.

PRECAUTIONS: General: Because of inherent suicide potential, dispense to severely depressed patients the smallest suitable amount of the drug. Manic depressive patients may experience a shift to the manic phase; schizophrenic patients may develop increased symptoms of psychosis; patients with paranoid symptomatology may have such symptoms exaggerated, requiring reduction of dosage or addition of a major tranquilizer to the therapeutic regimen. Antidepressant drugs can cause skin rashes and/or "drug fever" in susceptible individuals. These allergic reactions may, in rare cases, be severe. They are more likely to occur during the first few days of treatment, but may also occur later. ASENDIN® amoxapine should be discontinued if rash and/or fever develop. Amoxapine possesses a degree of dopamine-blocking activity which may cause extrapyramidal symptoms in <1% of patients. Rarely, symptoms indicative of tardive dyskinesia have been reported. Information for the patient: It is advised that all patients in whom chronic use of neuroleptic drugs is contemplated be given full information about the risk of tardive dyskinesia. Warn patients of possibility of decreased performance of potentially hazardous tasks such as driving an automobile or operating machinery may be impaired. Drug interactions: See Contraindications regarding concurrent use of tricyclic antidepressants and monoamine oxidase inhibitors. Paralytic ileus may occur when tricyclic antidepressants are taken in combination with anticholinergic drugs. ASENDIN may enhance response to alcohol and the effects of barbiturates and other CNS depressants. Serum levels of several tricyclic antidepressants have been reported to be significantly increased when cimetidine is administered concurrently. Although such an interaction has not been reported to date with ASENDIN, specific interaction studies have not been done, and the possibility should be considered. Therapeutic interactions: Concurrent administration with electroshock may increase hazards associated with such therapy. Carcinogenesis, impairment of fertility: In a 21-month toxicity study of three-dose levels in rats, pancreatic islet cell hyperplasia occurred with slightly increased incidence at doses 5-10 times the human dose. Pancreatic adenocarcinoma was detected in low incidence in the mid-dose group only, and may possibly have resulted from endocrine-mediated organ hyperfunction. The significance of these findings to man is not known. Treatment of male rats with 5-10 times the human dose resulted in a slight decrease in the number of fertile matings. Female rats receiving oral doses within the therapeutic range displayed a reversible increase in estrous cycle length. Pregnancy: Pregnancy Category C: Studies performed in mice, rats, and rabbits have demonstrated no evidence of teratogenic effect due to ASENDIN. Embryotoxicity was seen in rats and rabbits given oral doses approximating the human dose. Fetal effects (intrauterine death, stillbirth, decreased birth weight) were seen in animals studied at oral doses 3-10 times the human dose. Decreased postnatal survival (between days 0-4) was demonstrated in the offspring of rats at 5-10 times the human dose. These are not adequate and well-controlled studies of pregnant women. ASENDIN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Nursing mothers: ASENDIN, like many other systemic drugs, is excreted in human milk. Because effects of the drug on infants are unknown, caution should be exercised when ASENDIN is administered to nursing women. Pediatric use: Safety and effectiveness in children below the age of 16 have not been established.

ADVERSE REACTIONS: Reported in Controlled Studies: Incidence greater than 1%—Most frequent were sedative and anticholinergic—drowsiness (14%), dry mouth (14%), constipation (12%), and blurred vision (7%).

Less frequently reported reactions were: CNS and Neuromuscular—anxiety, insomnia, restlessness, nervousness, palpitations, tremors, confusion, excitement, nightmares, ataxia, alterations in EEG patterns. Allergic—edema, skin rash. Endocrine—elevation of prolactin levels. Gastrointestinal—nausea, dizziness, headache, fatigue, weakness, excessive appetite, increased perspiration. Incidence less than 1%—Anticholinergic—disturbances of accommodation, mydriasis, urinary retention, nasal stuffiness, cardiovascular—cardiac arrhythmias, hypotension, hypertension, syncope, tachycardia. Allergic—drug fever, urticaria, photosensitization, pruritus, rarely, vasculitis, hepatitis. CNS and Neuromuscular—tingling, paresthesias of the extremities, linitus, disorientation, seizures, hypomania, numbness, incoordination, disturbed concentration, hyperthermia, extrapyramidal symptoms, including, rarely, tardive dyskinesia. Neuroleptic malignant syndrome has been reported. Hematology—leukopenia, agranulocytosis. Gastrointestinal—epigastric distress, vomiting, flatulence, abdominal pain, peptic ulcer, diarrhea. Endocrine—decreased libido, impotence, menstrual irregularity, breast atrophy, galactorrhea in the female, syndrome of inappropriate antidiuretic hormone secretion. Other—lacrimation, weight gain or loss, altered liver function. Drug Relationship Unknown: Reported rarely, but under circumstances where drug relationship was unknown: Anticholinergic—paralytic ileus. Cardiovascular—atrial arrhythmias (including atrial fibrillation), myocardial infarction, stroke, heart block. CNS and Neuromuscular—hallucinations. Hematology—thrombocytopenia, eosinophilia, purpura, ptelechias. Gastrointestinal—parotid swelling. Endocrine—change in blood glucose levels. Other—pancreatitis, hepatitis, jaundice, urinary frequency, testicular swelling, anorexia, alopecia.

Additional Adverse Reactions Reported with Other Antidepressant Drugs: Anticholinergic—sublingual adenitis, dilation of the urinary tract. CNS and Neuromuscular—delusions. Gastrointestinal—stomatitis, black tongue. Endocrine—gynecomastia.

OVERDOSAGE: Signs and Symptoms

Toxic manifestations of ASENDIN® amoxapine overdosage differ significantly from those of other tricyclic antidepressants. Serious cardiovascular effects are seldom, if ever, observed. However, CNS effects—particularly grand mal convulsions—occur frequently, and treatment should be directed primarily toward prevention or control of seizures. Status epilepticus may develop and constitutes a neurologic emergency. Coma and acidosis are other serious complications of substantial ASENDIN overdosage. In some cases, renal failure may develop two to five days after toxic dosages, typically in those who have experienced multiple seizures.

Treatment

Treatment of ASENDIN overdosage should be symptomatic and supportive, but with special attention to prevention or control of seizures. Seizures may respond to standard anticonvulsive therapies, such as intravenous diazepam and/or phenytoin. The value of physostigmine appears less certain. Status epilepticus, should it develop, requires vigorous treatment such as that described by Delgado-Escueta, et al (N Engl J Med 1982; 306: 1337-1340).

Convulsions, when they occur, typically begin within 12 hours after ingestion. Prophylactic administration of anticonvulsant medication during this period may be of value. Treatment of renal failure, should it occur, is the same as that for non-drug-induced renal dysfunction. Serious cardiovascular effects are remarkably rare following ASENDIN overdosage, and the ECG typically remains within normal limits, except for sinus tachycardia. Hence, prolongation of the QRS interval beyond 100 milliseconds within the first 24 hours is not a useful guide to the severity of overdosage with this drug. Fatalities and, rarely, neurologic sequelae have resulted from prolonged status epilepticus in ASENDIN overdosage patients.

REFERENCES:

1. Hekimian LJ, Friedhoff AJ, Deever E: A comparison of the onset of action and therapeutic efficacy of amoxapine and amitriptyline. J Clin Psychiatry 1978;39:633-637.
2. Data on file, Lederle Laboratories, Pearl River, N.Y.
3. Hekimian LJ, Weise CG, Friedhoff AJ: Onset of action of amoxapine and doxepin in outpatients with "mixed anxiety depression." J Clin Psychiatry 1983; 44:248-252.
4. Paprocki J, Bustamante LS, Barcala Pelkolo MP et al: A double-blind comparison of amoxapine and imipramine in depression. A Folha Médica 1977; 74: 199-210.
5. Fabre LF: The treatment of depression in outpatients: A controlled comparison of the onset of action of amoxapine and maprotiline. J Clin Psychiatry. 1985;46:521-524.

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Calendar

(Continued from page A. 7)

Executive Vice-President, 2250 East Devon Ave., Suite 316, Des Plaines, IL 60018 312-297-3317.

April 9-11, semiannual meeting, Group for the Advancement of Psychiatry, White Plains, N.Y. Contact Michael E. Zales, M.D., President, P.O. Box 330, Greenbelt, MD 20770; 301-345-8030

April 15-20, Sixth International Conference, Adolescents in Crisis, Barbados, West Indies. Contact Pamela McMahon, Southern California Neuropsychiatric Institute, 6794 La Jolla Blvd., La Jolla, CA 92037; 619-454-2102.

April 17-18, annual meeting, Bulimia Anorexia Self-Help, Inc., St. Louis. Contact Felix E.F. Larocca, M.D., Executive Director, 6125 Clayton Ave., Suite 215, St. Louis, MO 63139; 314-567-4080.

April 22-24, 28th National Student Research Forum, University of Texas Medical Branch, Galveston, Tex. Contact National Student Research Forum, UTMB, P.O. Box 54—Station 1, Galveston, TX 77550; 409-761-3762.

April 22-25, annual meeting, American Association for Counseling and Development, New Orleans. Contact Patrick J. McDonough, Ed.D., Executive Director, 5999 Stevens Ave., Alexandria, VA 22304; 703-823-9800.

April 22-25, Fifth Annual Symposium in Psychiatry and Law, American College of Forensic Psychiatry, Monterey, Calif. Contact Ed Miller, Executive Director, 26701 Quail Creek, Suite 295, Laguna Hills, CA 92656; 714-831-0235.

April 22-27, annual meeting, National Council on Alcoholism, Inc., Cleveland. Contact Thomas V. Seesel, Executive Director, 12 West 21st St., 7th Fl., New York, NY 10011; 212-206-6770.

April 23-26, annual conference, American Medical Society on Alcoholism and Other Drug Dependencies, Cleveland. Contact Claire Osmar, AMAAODD Administrative Director, 12 West 21st St., New York, NY 10010; 212-206-6770.

April 26-28, part II examinations, American Board of Psychiatry and Neurology, Los Angeles. Contact Stephen M. Scheiber, M.D., Executive Secretary, Suite 808, 1 American Plaza, Evanston, IL 60201 312-864-0830.

April 26-May 1, annual meeting, American Occupational Medical Association, Philadelphia. Contact Donald L. Hoops, Ph.D., Executive Director, 2340 S. Arlington Heights Rd., Suite 400, Arlington Heights, IL 60005; 312-228-6851.

April 27-May 1, annual meeting, American Pediatric Socie-

ty, Anaheim, Calif. Contact Audrey Brown, M.D., Secretary, Dept. of Pediatrics, Box 49, Downstate Medical Center, 450 Clarkson Ave., Brooklyn, NY 11203; 718-270-1692.

April 29-May 2, annual meeting, American Association for the History of Medicine, Inc., Philadelphia. Contact Edward C. Atwater, M.D., Secretary-Treasurer, University of Rochester Medical Center, 601 Elmwood Ave., Rochester, NY 14642; 716-275-2903.

April 29-May 3, annual meeting, American Association of Pastoral Counselors, New Orleans. Contact James W. Ewing, Ph.D., Executive Director, 9508 A Lee Hwy., Fairfax, VA 22031; 703-385-6967.

MAY

May 1-4, annual meeting, American Federation for Clinical Research, Eastern Section, San Diego. Contact Robert K. Talley, Executive Secretary, Charles B. Slack, Inc., 6900 Grove Rd., Thorofare, NJ 08086; 609-848-1000.

May 6-10, annual meeting, American Psychoanalytic Association, Chicago. Contact Helen Fischer, Administrative Director, 309 East 49th St., New York, NY 10017; 212-752-0450.

May 6-10, annual meeting, Society of Biological Psychiatry, Chicago. Contact Philip A. Berger, M.D., Secretary-Treasurer, Dept. of Psychiatry, Stanford University School of Medicine, Stanford, CA 94305; 415-723-0852.

May 7-10, annual meeting, American Academy of Psychoanalysis, Chicago. Contact Vivian Mendelsohn, Executive Director, 30 East 40th St., Suite 608, New York, NY 10016; 212-679-4105.

May 8-10, annual meeting, American Society for Adolescent Psychiatry, Chicago. Contact Mary D. Staples, Executive Director, 24 Green Valley Rd., Wallingford, PA 19086; 215-566-1054.

May 9, annual meeting, American College of Psychoanalysts, Chicago. Contact Leo Madow, M.D., Secretary General, Institute of Pennsylvania Hospital, 111 North 49th St., Philadelphia, PA 19139; 215-471-2339.

May 9, annual meeting, American Society of Psychoanalytic Physicians, Chicago. Contact Mrs. Deborah C. Skolnik, Executive Director, 904 Dryden St., Silver Spring, MD 20901; 301-681-7385.



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WARNING

Lithium toxicity is closely related to serum lithium levels, and can occur at doses close to therapeutic levels. Facilities for prompt and accurate serum lithium determinations should be available before initiating therapy.

INDICATIONS

Lithium is indicated in the treatment of manic episodes of manic-depressive illness. Maintenance therapy prevents or diminishes the intensity of subsequent episodes in those manic-depressive patients with a history of mania.

Typical symptoms of mania include: pressure of speech, motor hyperactivity, reduced need for sleep, flight of ideas, grandiosity, elation, poor judgment, aggressiveness, and possibly hostility. When given to a patient experiencing a manic episode, lithium may produce a normalization of symptomatology within 1 to 3 weeks.

WARNINGS

Lithium should generally not be given to patients with significant renal or cardiovascular disease, severe dehydration or dehydration, or sodium depletion, and to patients receiving diuretics, since the risk of lithium toxicity is very high in such patients. If the psychiatric indication is life-threatening, and if such a patient fails to respond to other measures, lithium treatment may be undertaken with extreme caution, including daily serum lithium determinations and adjustment to the usually low doses ordinarily tolerated by these individuals. In such instances, hospitalization is a necessity.

Lithium toxicity is closely related to serum lithium levels, and can occur at doses close to therapeutic levels (see **DOSE AND ADMINISTRATION**).

Lithium therapy has been reported in some cases to be associated with morphologic changes in the kidneys. The relationship between such changes and renal function has not been established.

Outpatients and their families should be warned that the patient must discontinue lithium therapy and contact his physician if such clinical signs of lithium toxicity as diarrhea, vomiting, tremor, mild ataxia, drowsiness, or muscular weakness occur.

Lithium may impair mental and/or physical activities. Caution patients about activities requiring alertness (e.g., operating vehicles or machinery).

Usage in Pregnancy: Adverse effects on nidation in rats, embryo viability in mice, and metabolism *in vitro* of rat testis and human spermatozoa have been attributed to lithium. It has teratogenicity in submammalian species and cleft palates in mice. Studies in rats, rabbits and monkeys have shown no evidence of lithium-induced teratology.

There are lithium birth registries in the United States and elsewhere; however there are at the present time insufficient data to determine the effects of lithium on human fetuses. Therefore, at this point, lithium should not be used in pregnancy, especially the first trimester, unless in the opinion of the physician, the potential benefits outweigh the possible hazards.

Usage in Nursing Mothers: Lithium is excreted in human milk. Nursing should not be undertaken during lithium therapy except in rare and unusual circumstances where, in the view of the physician, the potential benefits to the mother outweigh possible hazards to the child.

Usage in Children: Since information regarding the safety and effectiveness of lithium in children under 12 years of age is not available, its use in such patients is not recommended at this time.

PRECAUTIONS

The ability to tolerate lithium is greater during the acute manic phase and decreases when manic symptoms subside (see **DOSE AND ADMINISTRATION**).

The distribution space of lithium approximates that of total body water. Lithium is primarily excreted in urine with insignificant excretion in feces. Renal excretion of lithium is proportional to its plasma concentration. The half-elimination time of lithium is approximately 24 hours. Lithium decreases sodium reabsorption by the renal tubules which could lead to sodium depletion. Therefore, it is essential that patients be maintained on a normal diet, including salt, and an adequate fluid intake (2500-3000 ml) at least during the initial stabilization period. Decreased tolerance to lithium has been

occure, supplemental fluid and salt should be administered.

In addition to sweating and diarrhea, concurrent infection with elevated temperatures may also necessitate a temporary reduction or cessation of medication.

Previously existing underlying disorders do not necessarily constitute a contraindication to lithium treatment, where hypothyroidism exists, careful monitoring of thyroid function during lithium stabilization and maintenance allows for correction of changing thyroid parameters. Tany, where hypothyroidism occurs during lithium stabilization and maintenance, supplemental thyroid treatment may be used.

Drug Interactions

Lithium may potentiate the effects of neuromuscular blocking agents, such as decamethonium, pancuronium, and succinylcholine. Therefore, neuromuscular blocking agents should be given with caution to patients receiving lithium.

Combined Use of Haloperidol and Lithium: An encephalopathic syndrome (characterized by weakness; lethargy; fever; tremulousness and confusion; ataxic pyramidal symptoms; leukocytosis; elevated serum enzymes, BUN, and fasting blood sugar), followed by irreversible brain damage, has occurred in a few patients treated with lithium plus haloperidol. A causal relationship between these events and the concurrent administration of lithium and haloperidol has not been established. However, patients receiving such combined therapy should be monitored closely for early evidence of neurological toxicity, and treatment discontinued promptly if such signs appear. The possibility of similar adverse interactions with other antipsychotic medications exists. In addition, concurrent use of lithium with chlorpromazine and possibly other phenothiazines decreases serum chlorpromazine levels as much as 40%.

Concomitant administration of carbamazepine and lithium may increase the risk of neurotoxic side effects.

Aminophylline, caffeine, dipyridine, oxtriphyline, sodium bicarbonate, or theophylline used concurrently may decrease the therapeutic effect of lithium because of its increased urinary excretion.

Concurrent use of diuretics, especially thiazides, with lithium may provoke lithium toxicity due to reduced renal clearance.

Concurrent use of iodide preparations, especially potassium iodide, with lithium may produce hypothyroidism.

Indomethacin (50 mg t.i.d.) has been reported to increase steady-state plasma lithium levels from 30 to 39 percent. There is also some evidence for other nonsteroidal, anti-inflammatory agents may have a similar effect. When such combinations are used, increased monitoring of plasma lithium levels is recommended.

ADVERSE REACTION

Adverse reactions are seldom encountered at serum lithium levels below 1.5 mEq/L except in the occasional patient sensitive to lithium. Mild-to-moderate toxic reactions may occur at levels from 1.5-2.5 mEq/L, and moderate-to-severe reactions may be seen at levels from 2.0-3.5 mEq/L, depending upon individual response to the drug.

Fine hand tremor, polyuria and mild thirst may occur during initial therapy. In the acute manic phase, and may persist throughout treatment. Transient and mild nausea and general discomfort may also appear during the first few days of lithium administration. These side effects are an inconvenience rather than a disabling condition, and usually subside with continued treatment or a temporary reduction or cessation of dosage. If persistent, a cessation of dosage is indicated.

Diarrhea, vomiting, drowsiness, muscular weakness and lack of coordination may be early signs of lithium intoxication, and can occur at lithium levels below 2.0 mEq/L. At higher levels, giddiness, ataxia, blurred vision, vertigo, and a large output of dilute urine may be seen. Serum lithium levels above 3.0 mEq/L may produce a complex clinical picture involving multiple organs and organ systems. Serum lithium levels should not be permitted to exceed 2.0 mEq/L during the acute treatment phase.

The following toxic reactions have been reported and appear to be related to serum lithium levels, including levels within the therapeutic range:

Neuromuscular: tremor, muscle hyperirritability, fasciculations, twitching, clonic movements of whole limbs, ataxia, choreoathetoid movements, hyperactive deep tendon reflexes.

Central Nervous System: blackout spells, epileptiform seizures, slurred speech, dizziness, vertigo, incontinence of urine or feces, somnolence, psychomotor retardation, restlessness, confusion, stupor, coma. Cases of pseudotumor cerebri (increased intracranial pressure and papilledema) have been reported with lithium use. If undetected, this condition may result in enlargement of the blind spot, constriction of visual fields, and eventual blindness due to optic atrophy. If this syndrome occurs, lithium should be discontinued if clinically possible.

Cardiovascular: cardiac arrhythmia, hypotension, peripheral circulatory collapse.

Gastrointestinal: anorexia, nausea, vomiting, diarrhea.

Genitourinary: albuminuria, oliguria, polyuria, glycosuria.

Dermatologic: dryness and thinning of hair, anesthesia of skin,



Autonomic Nervous System: blurred vision, dry mouth.

Miscellaneous: fatigue, lethargy, tendency to sleep, dehydration, weight loss, transient scotomata.

Thyroid Abnormalities: euthyroid goiter and/or hypothyroidism (including myxedema) accompanied by lower T₃ and T₄. Iodine uptake may be elevated (see **PRECAUTIONS**). Paradoxically, rare cases of hyperthyroidism have been reported.

EEG Changes: diffuse slowing, widening of frequency spectrum, potentiation and disorganization of background rhythm.

EKG Changes: reversible flattening, isoelectricity or inversion of T-waves.

Miscellaneous reactions unrelated to dosage are: transient electroencephalographic and electrocardiographic changes, leucocytosis, headache, diffuse nontoxic goiter with or without hypothyroidism, transient hyperglycemia, generalized pruritus with or without rash, cutaneous ulcers, albuminuria, worsening of organic brain syndromes, excessive weight gain, edematous swelling of ankles or wrists, and thirst or polyuria, sometimes resembling diabetes insipidus and metallic taste.

A single report has been received of the development of painful discoloration of fingers and toes and coldness of the extremities within one day of the starting of treatment of lithium. The mechanism through which these symptoms (resembling Raynaud's Syndrome) developed is not known. Recovery followed discontinuance.

DOSE AND ADMINISTRATION

Acute Mania: Optimal patient response can usually be established and maintained with the following dosages:

Lithobid 900 mg b.i.d. or 600 mg t.i.d. (1800 mg per day)

Cibalith-S 10 ml (2 teaspoons) (16 mEq of lithium) t.i.d.

Such doses will normally produce an effective serum lithium level ranging between 1.0 and 1.5 mEq/L. Dosage must be individualized according to serum levels and clinical response. Regular monitoring of the patient's clinical state and of serum lithium levels is necessary. Serum levels should be determined twice per week during the acute phase, and until the serum level and clinical condition of the patient have been stabilized.

Long-term Control: The desirable serum lithium levels are 0.6 to 1.2 mEq/L. Dosage will vary from one individual to another, but usually the following dosages will maintain this level:

Lithobid 900 mg to 1200 mg per day given in two or three divided doses.

Cibalith-S 5 ml (1 teaspoon) (8 mEq of lithium) t.i.d. or q.i.d.

Serum lithium levels in uncomplicated cases receiving maintenance therapy during remission should be monitored at least every two months. Patients abnormally sensitive to lithium may exhibit toxic signs at serum levels of 1.0 to 1.5 mEq/L. Elderly patients often respond to reduced dosage, and may exhibit signs of toxicity at serum levels ordinarily tolerated by other patients.

N.B.: Blood samples for serum lithium determinations should be drawn immediately prior to the next dose when lithium concentrations are relatively stable (i.e., 8-12 hours after previous dose). Total reliance must not be placed on serum levels alone. Accurate patient evaluation requires both clinical and laboratory analysis.

Lithobid slow-release tablets must be swallowed whole and never crushed or chewed.

OVERDOSAGE

The toxic levels for lithium are close to the therapeutic levels. It is therefore important that patients and their families be cautioned to watch for early toxic symptoms and to discontinue the drug and inform the physician should they occur. Toxic symptoms are listed in detail under **ADVERSE REACTIONS**.

Treatment: No specific antidote for lithium poisoning is known. Early symptoms of lithium toxicity can usually be treated by reduction or cessation of dosage of the drug and resumption of the treatment at a lower dose after 24 to 48 hours. In severe cases of lithium poisoning, the first and foremost goal of treatment consists of elimination of this ion from the patient.

Treatment is essentially the same as that used in barbiturate poisoning: 1) gastric lavage 2) correction of fluid and electrolyte imbalance and 3) regulation of kidney functioning. Urea, mannitol, and aminophylline all produce significant increases in lithium excretion. Hemodialysis is an effective and rapid means of removing the ion from the severely toxic patient. Infection prophylaxis, regular chest x-rays, and preservation of adequate respiration are essential.

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Contact: Adigala Laxmi, M.D., Acting Clinical Dir., Middletown Psychiatric Center, Office of Mental Health, P.O. Box 1453, Middletown, New York 10940, (914) 342-5511, extension 3667.

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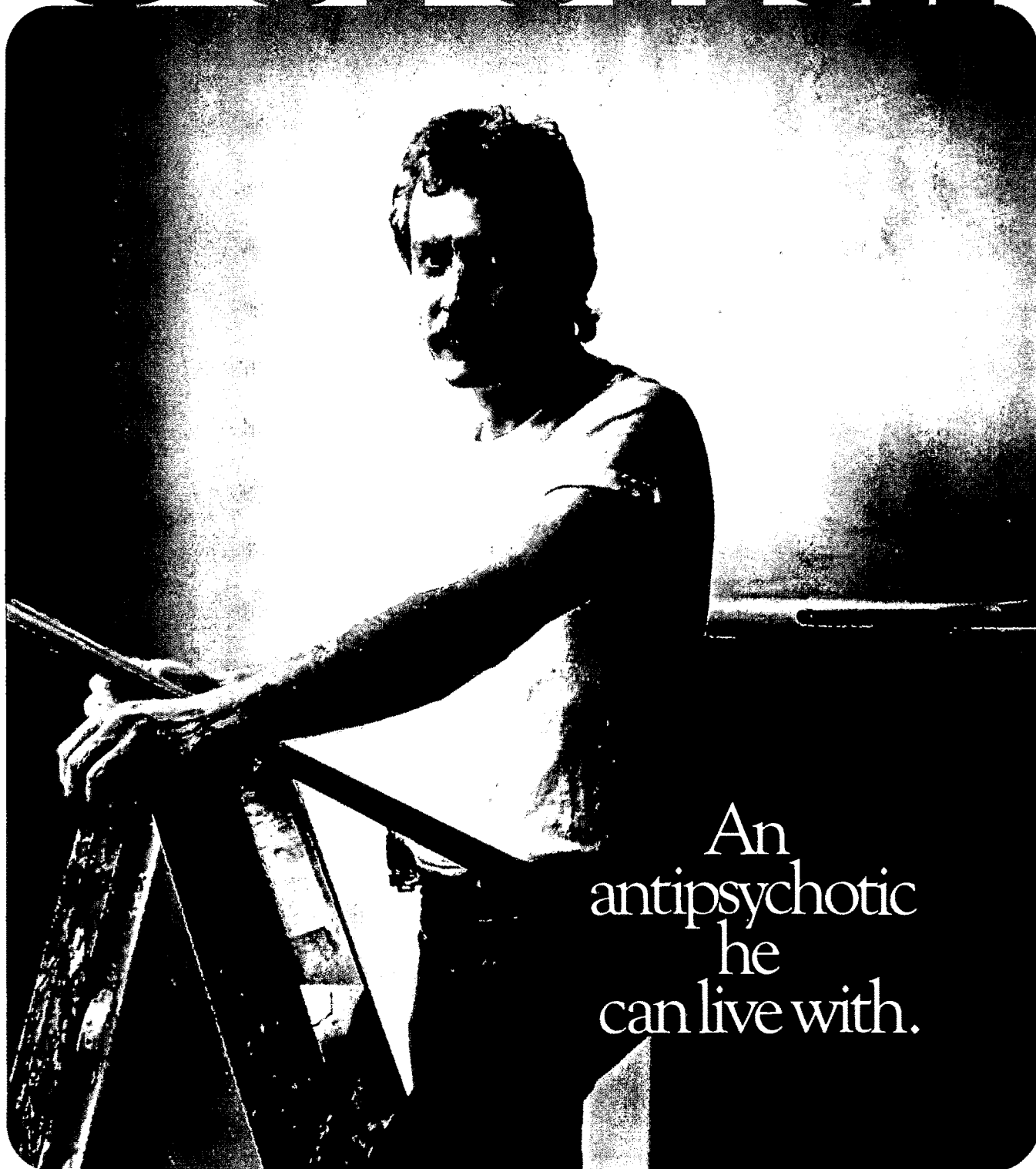
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(mesoridazine) as the besylate
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Please see following page for brief summary of prescribing information

Serentil® (mesoridazine) as the besylate

(mesoridazine) besylate tablets USP
(mesoridazine) besylate injection USP
(mesoridazine) besylate oral solution USP



Tablets: 25, 50 and 100 mg



Concentrate: 25 mg/ml



Injectable: 1 ml (25 mg)

Brief Summary of Prescribing Information

Contraindications: As with other phenothiazines, Serentil® (mesoridazine), is contraindicated in severe central nervous system depression or comatose states from any cause. Serentil is contraindicated in individuals who have previously shown hypersensitivity to the drug.

Warnings: *Tardive Dyskinesia:* Tardive dyskinesia, a syndrome consisting of essentially irreversible, involuntary, dyskinetic movements may develop in patients treated with neuroleptic (antipsychotic) drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of neuroleptic treatment, which patients are likely to develop the syndrome. Whether neuroleptic drug products differ in their potential to cause tardive dyskinesia is unknown.

Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of neuroleptic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if neuroleptic treatment is withdrawn. Neuroleptic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying disease process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, neuroleptics should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic neuroleptic treatment should generally be reserved for patients who suffer from a chronic illness 1) the is known to respond to neuroleptic drugs, and 2) for which alternative, equally effective but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on neuroleptic drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome.

(For further information about the description of tardive dyskinesia and its clinical detection, please refer to the sections on Information for Patients and Adverse Reactions.) Where patients are participating in activities requiring complete mental alertness (e.g., driving) it is advisable to administer the phenothiazines cautiously and to increase the dosage gradually.

Usage in Pregnancy: The safety of this drug in pregnancy has not been established; hence, it should be given only when the anticipated benefits to be derived from treatment exceed the possible risks to mother and fetus.

Usage in Children: The use of Serentil (mesoridazine) in children under 12 years of age is not recommended, because safe conditions for its use have not been established. Attention should be paid to the fact that phenothiazines are capable of potentiating central nervous system depressants (e.g., anesthetics, opiates, alcohol, etc.) as well as atropine and phosphorus insecticides.

Precautions: While ocular changes have not to date been related to Serentil® (mesoridazine), one should be aware that such changes have been seen with other drugs of this class.

Because of possible hypotensive effects, reserve parenteral administration for fast patients or for acute ambulatory cases, and keep patient lying down for at least one-half hour after injection.

Leukopenia and/or agranulocytosis have been attributed to phenothiazine therapy. A single case of transient granulocytopenia has been associated with Serentil. If severe convulsive seizures have been reported, patients receiving anticonvulsant medication should be maintained on that regimen while receiving Serentil.

Neuroleptic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent in vitro, a factor of potential importance in the prescription of these drugs to a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of neuroleptic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time.

Information for Patients: Given the likelihood that some patients exposed chronically to neuroleptics will develop tardive dyskinesia, it is advised that all patients in whom chronic use is contemplated be given, if possible, full information about this risk.

Adverse Reactions: Drowsiness and hypotension were the most prevalent side effects encountered. Side effects tended to reach their maximum level of severity early in the exception of a few (rigidity and motor effects) which occurred later in therapy. With the exceptions of tremor and rigidity, adverse reactions were generally found among those patients who received relatively high doses early in treatment. Clinical data showed no tendency for the investigators to terminate treatment because of side effects. Serentil® (mesoridazine) has demonstrated a remarkably low incidence of adverse

reactions when compared with other phenothiazine compounds. **Central Nervous System:** Drowsiness, Parkinson's syndrome, dizziness, weakness, tremor, restlessness, ataxia, dystonia, rigidity, slurring, akathisia, motoric reactions (opisthotonos) have been reported.

Autonomic Nervous System: Dry mouth, nausea and vomiting, fainting, stuffy nose, photophobia, constipation and blurred vision have occurred in some instances.

Genitourinary System: Inhibition of ejaculation, impotence, enuresis, incontinence have been reported.

Skin: Itching, rash, hypertrophic papillae of the tongue and angioneurotic edema have been reported.

Cardiovascular System: Hypotension and tachycardia have been reported. EKG changes have occurred in some instances (see Phenothiazine Derivatives: Cardiovascular Effects).

Phenothiazine Derivatives: It should be noted that efficacy, indications and untoward effects have varied with the different phenothiazines. The physician should be aware that the following have occurred with one or more phenothiazines and should be considered whenever one of these drugs is used:

Autonomic Reactions: Miosis, obstipation, anorexia, paralytic ileus.

Cutaneous Reactions: Erythema, exfoliative dermatitis, contact dermatitis.

Blood Dyscrasias: Agranulocytosis, leukopenia, eosinophilia, thrombocytopenia, anemia, aplastic anemia, pancytopenia.

Allergic Reactions: Fever, laryngeal edema, angioneurotic edema, asthma.

Hepatotoxicity: Jaundice, biliary stasis.

Cardiovascular Effects: Changes in the terminal portion of the electrocardiogram,

including prolongation of the Q-T interval, lowering and inversion of the T wave and appearance of a wave tentatively identified as a bifid T or a U wave have been observed in some patients receiving the phenothiazine tranquilizers, including Serentil® (mesoridazine). To date, these appear to be due to altered repolarization and not related to myocardial damage. They appear to be reversible. While there is no evidence at present that these changes are in any way precursors of any significant disturbance of cardiac rhythm, it should be noted that sudden and unexpected deaths apparently due to cardiac arrest have occurred in patients previously showing characteristic electrocardiographic changes while taking the drug. The use of periodic electrocardiograms has been proposed but would appear to be of questionable value as a predictive device. Hypotension, rarely resulting in cardiac arrest, has been noted.

Extrapyramidal Symptoms: Akathisia, agitation, motor restlessness, dystonic reactions, trismus, torticollis, opisthotonos, oculogyric crises, tremor, muscular rigidity, akinesia.

Tardive Dyskinesia: Chronic use of neuroleptics may be associated with the development of tardive dyskinesia. The salient features of this syndrome are described in the Warnings section and below.

The syndrome is characterized by involuntary choreoathetoid movements which variously involve the tongue, face, mouth, lips, or jaw (e.g., protrusion of the tongue, puffing of cheeks, smacking of the mouth, chewing movements), trunk and extremities. The severity of the syndrome and the degree of impairment produced vary widely.

The syndrome may become clinically recognizable either during treatment, upon dosage reduction or upon withdrawal of treatment. Movements may decrease in intensity and may disappear altogether if further treatment with neuroleptics is withheld. It is generally believed that reversibility is more likely after short rather than long-term neuroleptic exposure. Consequently, early detection of tardive dyskinesia is important. To increase the likelihood of detecting the syndrome at the earliest possible time, the dosage of neuroleptic drug should be reduced periodically (if clinically possible) and the patient observed for signs of the disorder. This maneuver is critical, for neuroleptic drugs may mask the signs of the syndrome.

Endocrine Disturbances: Menstrual irregularities, altered libido, gynecomastia, lactation, weight gain, edema. False positive pregnancy tests have been reported.

Urinary Disturbances: Retention, incontinence.

Others: Hyperpyrexia. Behavioral effects suggestive of a paradoxical reaction have been reported. These include excitement, bizarre dreams, aggravation of psychoses and toxic confusion states. More recently, a peculiar skin-eye syndrome has been recognized as a side effect following long-term treatment with phenothiazines. This reaction is marked by progressive pigmentation of areas of the skin or conjunctiva and/or accompanied by discoloration of the exposed sclera and cornea. Opacities of the anterior lens and cornea described as irregular or stellate in shape have also been reported. Systemic lupus erythematosus-like syndrome.

How Supplied:

Serentil® tablets, for oral administration: 10 mg, 25 mg, 50 mg, and 100 mg mesoridazine (as the besylate). Bottles of 100.

Serentil® ampoules, for intramuscular administration: 1 ml (25 mg mesoridazine (as the besylate)) boxes of 20 and 100.

Serentil® concentrate, for oral administration: Contains 25 mg mesoridazine (as the besylate) per ml, alcohol, USP, 0.61% by volume.

Immediate containers: Amber glass bottles of 4 fl oz (118 ml) packaged in cartons of 12 bottles, with an accompanying dropper graduated to deliver 10 mg, 25 mg and 50 mg of mesoridazine (as the besylate).

Consult package insert before prescribing.

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1. Stone AA: Mental Health and Law: A System in Transition. Rockville, Md, NIMH, 1975, pp 102-103
2. Glick ID, Hargreaves WA, Drues J, et al: Short versus long hospitalization, a prospective controlled study, VII: two year follow-up results for nonschizophrenics. Arch Gen Psychiatry 1977; 34:314-320
3. Rubinow DR, Post RM, Pickar D, et al: Relationship between urinary-free cortisol and CSF opiate binding activity in depressed patients and normal volunteers. Psychiatry Research (in press)
4. McNamara JR (ed): Behavioral Approaches to Medicine. New York, Plenum Press, 1979
5. Janowsky DS, Judd LL, Huey L, et al: Effects of naloxone in normal, manic and schizophrenic patients: evidence for alleviation of manic symptoms, in Endorphins in Mental Health

Research. Edited by Usdin E, Bunney WE Jr, Kline NE. New York, Oxford University Press, 1979

6. Smythe GA, Compton PJ, Lazarus L: Serotonergic control of human growth hormone secretion: the actions of L-dopa and 5-bromo- α -ergocryptine. *Excerpta Medica International Congress Series* 1976; 381:222-235

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1. Grinspoon L (ed). Care and treatment of schizophrenia—Part II, in *The Harvard Medical School Mental Health Letter* 1986, 3(1): 1.

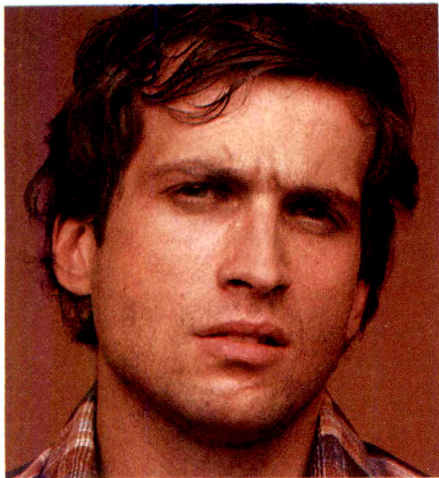
Patient portrayed by professional model

Please see brief summary of Prescribing Information on the next page.

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Contraindications: Severe, toxic CNS depression or comatose states from any cause, hypersensitivity to the drug, Parkinson's disease.

Warnings: Tardive Dyskinesia: Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with neuroleptic (antipsychotic) drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of neuroleptic treatment, which patients are likely to develop the syndrome. Whether neuroleptic drug products differ in their potential to cause tardive dyskinesia is unknown. Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of neuroleptic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. There is no known treatment for established cases of tardive dyskinesia. Neuroleptic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown. Given these considerations, neuroleptics should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic neuroleptic treatment should generally be reserved for patients who suffer from a chronic illness that, 1) is known to respond to neuroleptic drugs, and, 2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically. If signs and symptoms of tardive dyskinesia appear in a patient on neuroleptics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome. (For further information about the description of tardive dyskinesia and its clinical detection, please refer to ADVERSE REACTIONS.)

Usage in Pregnancy: Safe use in pregnancy or in women likely to become pregnant has not been established; use only if benefit clearly justifies potential hazards. Infants should not be nursed during drug treatment.

Combined Use With Lithium: Patients receiving lithium plus haloperidol should be monitored closely for early evidence of neurological toxicity and treatment discontinued promptly if such signs appear.

General: Bronchopneumonia, sometimes fatal, has followed use of major tranquilizers, including haloperidol. Prompt remedial therapy should be instituted if dehydration, hemoconcentration or reduced pulmonary ventilation occurs, especially in the elderly. Decreased serum cholesterol and/or cutaneous and ocular changes have been reported with chemically-related drugs, although not with haloperidol. Mental and/or physical abilities required for hazardous tasks or driving may be impaired. Alcohol should be avoided due to possible additive effects and hypotension.

Precautions: Administer cautiously to patients: (1) with severe cardiovascular disorders, due to the possibility of transient hypotension and/or precipitation of anginal pain (if a vasopressor is required, epinephrine should not be used since HALDOL may block its vasopressor activity and paradoxical further lowering of blood pressure may occur); (2) receiving anticonvulsant medications, with a history of seizures, or with EEG abnormalities, because HALDOL may lower the convulsive threshold. If indicated, adequate anticonvulsant therapy should be concomitantly maintained; (3) with known allergies or a history of allergic reactions to drugs; (4) receiving anticoagulants, since an isolated instance of interference occurred with the effects of one anticoagulant (phenindione). Concomitant antiparkinson medication, if required, may have to be continued after HALDOL is discontinued because of different excretion rates; if both are discontinued simultaneously, extrapyramidal symptoms may occur. Intraocular pressure may increase when anticholinergic drugs, including antiparkinson drugs, are administered concomitantly with HALDOL. When HALDOL is used for mania in cyclic disorders, there may be a rapid mood swing to depression. Severe neurotoxicity may occur in patients with thyrotoxicosis receiving antipsychotic medication, including HALDOL.

Carcinogenicity studies using oral haloperidol were conducted in Wistar rats (dosed at up to 5 mg/kg daily for 24 months) and in Albino Swiss mice (dosed at up to 5 mg/kg daily for 18 months). In the rat study survival was less than optimal in all dose groups, reducing the number of rats at risk for developing tumors. However, although a relatively greater number of rats survived to the end of the study in high dose male and female groups, these animals did not have a greater incidence of tumors than control animals. Therefore, although not optimal, this study does suggest the absence of a haloperidol-related increase in the incidence of neoplasia in rats at doses up to 20 times the usual daily human dose for chronic or resistant patients. In female mice at 5 and 20 times the highest initial daily dose for chronic or resistant patients, there was a statistically significant increase in mammary gland neoplasia and total tumor incidence; at 20 times the same daily dose there was a statistically significant increase in pituitary gland neoplasia. In male mice, no statistically significant differences in incidences of total tumors or specific tumor types were noted.

Neuroleptic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent in vitro, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in

rodents after chronic administration of neuroleptic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time. The 1, 5, 10 mg tablets contain FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible individuals, especially in those who have aspirin hypersensitivity.

Adverse Reactions: CNS Effects: Extrapyramidal Reactions: Neuromuscular (extrapyramidal) reactions have been reported frequently, often during the first few days of treatment. Generally they involved Parkinson-like symptoms which were usually mild to moderately severe and usually reversible. Other types of neuromuscular reactions (motor restlessness, dystonia and tardive dyskinesia, akathisia, hyperreflexia, opisthotonos, oculogyric crises) have been reported far less frequently, but were often more severe. Severe extrapyramidal reactions have been reported at relatively low doses. Generally, extrapyramidal symptoms are dose-related since they occur at relatively high doses and disappear or become less severe when the dose is reduced. Antiparkinson drugs may be required. Persistent extrapyramidal reactions have been reported and the drug may have to be discontinued in such cases.

Withdrawal Emergent Neurological Signs: Abrupt discontinuation of short-term antipsychotic therapy is generally uneventful. However, some patients on maintenance treatment experience transient dyskinetic signs after abrupt withdrawal. In certain cases these are indistinguishable from "Tardive Dyskinesia" except for duration. It is unknown whether gradual withdrawal will reduce the occurrence of these signs, but until further evidence is available HALDOL should be gradually withdrawn.

Tardive Dyskinesia: As with all antipsychotic agents HALDOL has been associated with persistent dyskinesias. Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may appear in some patients on long-term therapy or may occur after drug therapy has been discontinued. The risk appears to be greater in elderly patients on high-dose therapy, especially females. The symptoms are persistent and in some patients appear irreversible. The syndrome is characterized by rhythmic involuntary movements of tongue, face, mouth or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities. There is no known effective treatment for tardive dyskinesia; antiparkinson agents usually do not alleviate the symptoms of this syndrome. It is suggested that all antipsychotic agents be discontinued if these symptoms appear. Should it be necessary to reinstitute treatment, or increase the dosage of the agent, or switch to a different antipsychotic agent, this syndrome may be masked. It has been reported that fine vermicular movement of the tongue may be an early sign of the syndrome and if the medication is stopped at that time the syndrome may not develop.

Other CNS Effects: Insomnia, restlessness, anxiety, euphoria, agitation, drowsiness, depression, lethargy, headache, confusion, vertigo, grand mal seizures, and exacerbation of psychotic symptoms including hallucinations, and catatonic-like behavioral states which may be responsive to drug withdrawal and/or treatment with anticholinergic drugs.

Body as a Whole: Neuroleptic Malignant Syndrome: As with other neuroleptic drugs, a symptom complex sometimes referred to as neuroleptic malignant syndrome (NMS) has been reported. Cardinal features of NMS are hyperpyrexia, muscle rigidity, altered mental status (including catatonic signs), and evidence of autonomic instability (irregular pulse or blood pressure). Additional signs may include elevated CPK, myoglobinuria (rhabdomyolysis), and acute renal failure. NMS is potentially fatal, requires intensive symptomatic treatment and immediate discontinuation of neuroleptic treatment. Hyperpyrexia and heat stroke, not associated with the above symptom complex, have also been reported. **Cardiovascular Effects:** Tachycardia, hypotension, hypertension and ECG changes. **Hematologic Effects:** Reports of mild, usually transient leukopenia and leukocytosis, minimal decreases in red blood cell counts, anemia, or a tendency toward lymphomonocytosis, agranulocytosis rarely reported and only in association with other medication. **Liver Effects:** Impaired liver function and/or jaundice reported. **Dermatologic Reactions:** Maculopapular and acneiform reactions, isolated cases of photosensitivity, loss of hair. **Endocrine Disorders:** Lactation, breast engorgement, mastalgia, menstrual irregularities, gynecomastia, impotence, increased libido, hyperglycemia, hypoglycemia and hyponatremia. **Gastrointestinal Effects:** Anorexia, constipation, diarrhea, hypersalivation, dyspepsia, nausea and vomiting. **Autonomic Reactions:** Dry mouth, blurred vision, urinary retention and diaphoresis. **Respiratory Effects:** Laryngospasm, bronchospasm and increased depth of respiration. **Special Senses:** Cataracts, retinopathy and visual disturbances. **Other:** Cases of sudden and unexpected death have been reported in association with the administration of HALDOL. The nature of the evidence makes it impossible to determine definitively what role, if any, HALDOL played in the outcome of the reported cases. The possibility that HALDOL caused death cannot, of course, be excluded, but it is to be kept in mind that sudden and unexpected death may occur in psychotic patients when they go untreated or when they are treated with other neuroleptic drugs.

IMPORTANT: Full directions for use should be read before HALDOL haloperidol is administered or prescribed.

The injectable form is intended only for acutely agitated psychotic patients with moderately severe to very severe symptoms. Controlled trials to establish the safety and effectiveness of intramuscular administration in children have not been conducted.

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WARNINGS — Not recommended for use in depressive neuroses or psychotic reactions. Caution patient against hazardous occupations requiring mental alertness, such as operating dangerous machinery including motor vehicles. Advise against simultaneous use of other CNS depressants, and caution patients that effects of alcohol may be increased. Not recommended for patients under 9. Nervousness, insomnia, irritability, diarrhea, muscle aches, and memory impairment have followed abrupt withdrawal from long-term high dosage. Withdrawal symptoms were reported after abrupt discontinuance of benzodiazepines taken continuously at therapeutic levels for several months. Use caution in patients having psychological potential for drug dependence (dependence has been observed in dogs and rabbits).

Pregnancy and Lactation: Minor tranquilizers should almost always be avoided during first trimester. Consider possibility of pregnancy before initiating therapy. Patient should consult physician about discontinuation if she becomes pregnant or plans pregnancy. Do not give to nursing mothers.

PRECAUTIONS — Observe usual precaution in depression accompanying anxiety, or in patients with suicidal tendency, or those with impaired renal or hepatic function. Do periodic blood counts and liver function tests during prolonged therapy. Use small doses and gradual increments in the elderly or debilitated.

ADVERSE REACTIONS — Drowsiness, dizziness, various g.i. complaints, nervousness, blurred vision, dry mouth, headache, mental confusion, insomnia, transient skin rashes, fatigue, ataxia, genitourinary complaints, irritability, diplopia, depression, slurred speech, abnormal liver and kidney function tests, decreased hematocrit, decreased systolic blood pressure.

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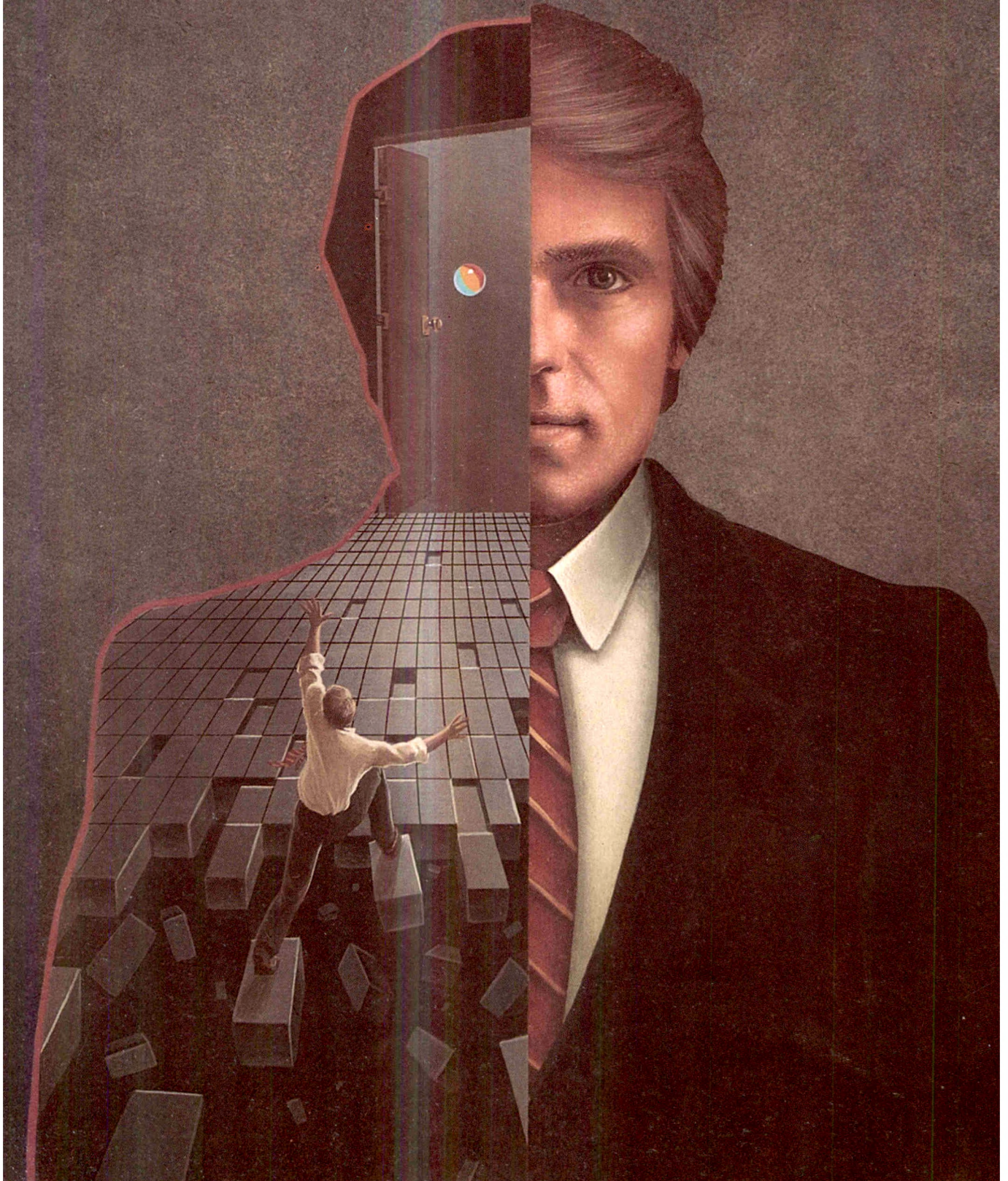
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Before prescribing, see complete prescribing information in SK&F Co. literature or PDR. The following is a brief summary.

Contraindications: Comatose or greatly depressed states due to C.N.S. depressants, blood dyscrasias, bone marrow depression, liver damage.

Warnings: Tardive dyskinesia (TD) may develop in patients treated with neuroleptic (anti-psychotic) drugs. The risk of TD and likelihood of irreversibility are thought to increase as duration of treatment and total cumulative neuroleptic dose increase. Much less commonly, the syndrome can develop after relatively brief treatment at low doses. There is no known treatment for TD, although it may remit if neuroleptics are withdrawn. Neuroleptic treatment may suppress signs and symptoms of the syndrome and thereby mask the underlying disease process. To minimize risk of TD, generally reserve chronic neuroleptic treatment for patients who suffer from chronic illness that responds to neuroleptics and for whom alternative, effective, less harmful treatments are not available or appropriate. In patients requiring chronic treatment, the minimal effective dose and shortest duration of treatment should be sought. Periodically reassess need for continued treatment. If signs and symptoms of TD appear, discontinuation of neuroleptics should be considered. [See PRECAUTIONS.]

Generally avoid using in patients hypersensitive (e.g., have had blood dyscrasias, jaundice) to any phenothiazine. Caution patients about activities requiring alertness (e.g., operating vehicles or machinery), especially during the first few days' therapy. Additive depressant effect is possible with other C.N.S. depressants, including alcohol. Do not use in pregnancy except when essential and potential benefits clearly outweigh possible hazards. Prolonged jaundice, extrapyramidal signs, hyperreflexia and hyporeflexia have been reported in newborns whose mothers received phenothiazines. There is evidence that phenothiazines are excreted in the breast milk of nursing mothers.

Precautions: Since some patients chronically exposed to neuroleptics will develop tardive dyskinesia, it is advised that, if possible, full information about this risk be given to patients or their guardians when chronic use is contemplated.

Use cautiously in angina. Avoid high doses and parenteral use when cardiovascular system is impaired since hypotension has occurred. Antiemetic effect may mask the signs of overdosage of other drugs or obscure diagnosis and treatment of certain physical disorders. Prolonged use of high doses may result in cumulative effects with severe C.N.S. or vasomotor symptoms. If retinal changes occur, discontinue drug. Agranulocytosis, thrombocytopenia, pancytopenia, anemia, cholestatic jaundice, liver damage have been reported. Use cautiously in patients with glaucoma.

Patients with a history of long-term therapy with 'Stelazine' and/or other neuroleptics should be evaluated periodically for possible dosage adjustment or discontinuance of drug therapy. Neuroleptic drugs cause elevated prolactin levels that persist during chronic use. Since approximately one-third of human breast cancers are prolactin-dependent *in vitro*, this elevation is of potential importance if neuroleptic drug use is contemplated in a patient with a previously detected breast cancer. However, clinical and epidemiologic studies to date have not shown an association between the chronic use of neuroleptic drugs and mammary tumorigenesis. Use cautiously in persons who will be exposed to extreme heat.

Phenothiazines may diminish the effect of oral anticoagulants. Phenothiazines can produce alpha-adrenergic blockade. Concomitant use of phenothiazines with propranolol increases plasma levels of both drugs. Concurrent use of phenothiazines may counteract antihyperten-

sive effects of guanethidine and related compounds. Thiazide diuretics may accentuate the orthostatic hypotension that may occur with phenothiazines. Phenothiazines may lower the convulsive threshold and may also precipitate phenytoin toxicity; dosage adjustments of anticonvulsants may be necessary. If neuromuscular reactions occur in pregnant women, or in children, permanently stop neuroleptic therapy. Patients should not receive 'Stelazine' 48 hours before or 24 hours after myelography with the contrast medium metrizamide. The presence of phenothiazines may produce false positive phenylketonuria (PKU) test results.

Adverse Reactions: Drowsiness, dizziness, skin reactions, rash, dry mouth, insomnia, amenorrhea, fatigue, muscular weakness, anorexia, lactation, blurred vision. Neuromuscular (extrapyramidal) reactions: motor restlessness, dystonias, pseudo-parkinsonism, tardive dyskinesia; and a variant, tardive dystonia.

Other adverse reactions reported with Stelazine (trifluoperazine HCl, SK&F) or other phenothiazines: Some adverse effects are more frequent or intense in specific disorders (e.g., mitral insufficiency or pheochromocytoma).

Grand mal and petit mal convulsions, particularly in the presence, or with history of EEG abnormalities; altered cerebrospinal fluid proteins; cerebral edema; prolongation and intensification of the action of C.N.S. depressants, atropine, heat, and organophosphorus insecticides; nasal congestion, headache, nausea, constipation, obstipation, adynamic ileus, ejaculatory disorders/impotence, priapism, atonic colon, urinary retention, miosis and mydriasis; reactivation of psychotic processes, catatonic-like states, hypotension (sometimes fatal); cardiac arrest; leukopenia, eosinophilia, pancytopenia, agranulocytosis, thrombocytopenic purpura, hemolytic anemia, aplastic anemia, jaundice, biliary stasis, hyperglycemia, hypoglycemia, glycosuria, menstrual irregularities, galactorrhea, gynecomastia, false positive pregnancy tests, photosensitivity: itching, erythema, urticaria, eczema up to exfoliative dermatitis, asthma, laryngeal edema, angioneurotic edema, anaphylactoid reactions, peripheral edema; reversed epinephrine effect; hyperpyrexia; mild fever after large I.M. doses; increased appetite; increased weight; a systemic lupus erythematosus-like syndrome; pigmentary retinopathy, with prolonged administration of substantial doses, skin pigmentation, epithelial keratopathy, and lenticular and corneal deposits; neuroleptic malignant syndrome, which may be fatal; EKG changes—particularly nonspecific, usually reversible Q and T wave distortions—have been observed. Temporary nausea, vomiting, dizziness, and tremulousness may follow abrupt cessation of high-dose therapy. NOTE: Sudden death in patients taking phenothiazines (apparently due to cardiac arrest or asphyxia due to failure of cough reflex) has been reported.

Supplied: Tablets, 1 mg., 2 mg., 5 mg. and 10 mg., in bottles of 100 and 1000; in Single Unit Packages of 100 (intended for institutional use only); Injection, 2 mg./ml., and Concentrate (intended for institutional use only), 10 mg./ml.

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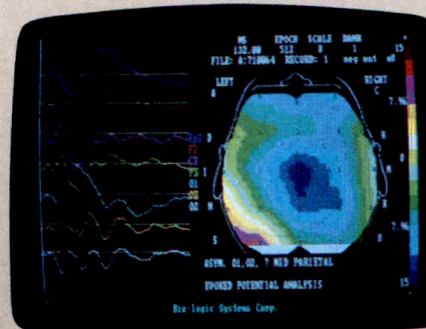
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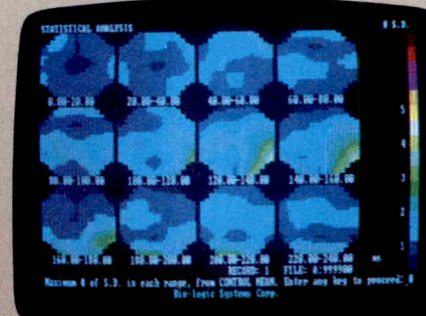
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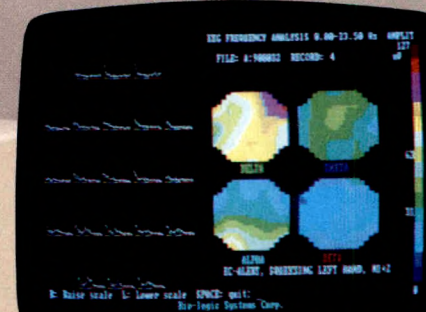
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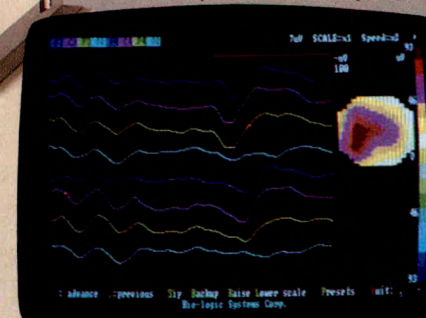
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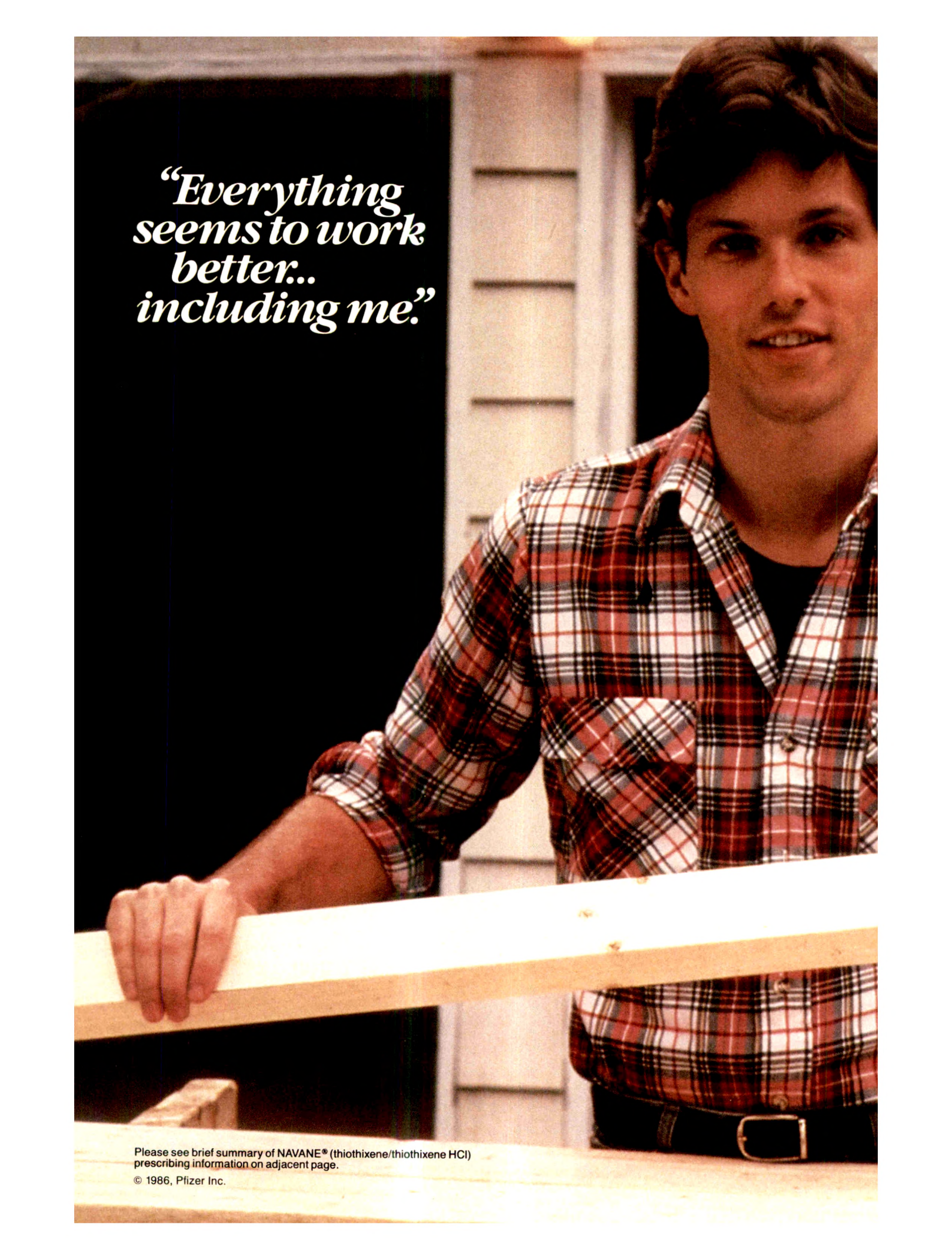
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References: 1 Bressler B, Friedel RD: A comparison between chlorpromazine and thiothixene in a Veterans Administration hospital population. *Psychosomatics* 1971;12:275-277. 2 DiMascio A, Demigian E: Study of the activating properties of thiothixene. *Psychosomatics* 1972;13:105-108. 3 DiMascio A, Demigian E: Job training in the rehabilitation of the chronic schizophrenic. Presented as a Scientific Exhibit at The American Psychiatric Association, Washington, DC, May 3-6, 1971. 4 Goldstein B, Weiner D, Banas F: Clinical evaluation of thiothixene in chronic ambulatory schizophrenic patients. In Lehmann HE, Ban TA (eds): *The Thioxanthenes: Modern Problems of Pharmacopsychiatry*. Basel, Switzerland, S Karger, 1969, vol 2, pp 45-52. 5 Dillenkoff RL, Gallant DM, George RB, et al: Electrocardiographic evaluation of schizophrenic patients: A double-blind comparison. Presented as a Scientific Exhibit at The 125th Annual Meeting of The American Psychiatric Association, Dallas, May 1-4, 1972. 6 Data available on request from Roerig.

BRIEF SUMMARY OF PRESCRIBING INFORMATION

Navane® (thiothixene) Capsules: 1 mg, 2 mg, 5 mg, 10 mg, 20 mg
(thiothixene hydrochloride) Concentrate: 5 mg/ml, intramuscular: 2 mg/ml, 5 mg/ml

Contraindications: Navane (thiothixene) is contraindicated in patients with circulatory collapse, comatose states, central nervous system depression due to any cause, and blood dyscrasias. Navane is contraindicated in individuals who have shown hypersensitivity to the drug. It is not known whether there is a cross-sensitivity between the thioxanthenes and the phenothiazine derivatives, but the possibility should be considered.

Warnings: *Tardive Dyskinesia*—Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with neuroleptic (antipsychotic) drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of neuroleptic treatment, which patients are likely to develop the syndrome. Whether neuroleptic drug products differ in their potential to cause tardive dyskinesia is unknown.

Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of neuroleptic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if neuroleptic treatment is withdrawn. Neuroleptic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying disease process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, neuroleptics should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic neuroleptic treatment should generally be reserved for patients who suffer from a chronic illness that, 1) is known to respond to neuroleptic drugs, and, 2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on neuroleptics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome.

(For further information about the description of tardive dyskinesia and its clinical detection, please refer to the section on Adverse Reactions.)

Usage in Pregnancy—Safe use of Navane during pregnancy has not been established. Therefore, this drug should be given to pregnant patients only when, in the judgment of the physician, the expected benefits from the treatment exceed the possible risks to mother and fetus. Animal reproduction studies and clinical experience to date have not demonstrated any teratogenic effects.

In the animal reproduction studies with Navane, there was some decrease in conception rate and litter size, and an increase in resorption rate in rats and rabbits, changes which have been similarly reported with other psychotropic agents. After repeated oral administration of Navane to rats (5 to 15 mg/kg/day), rabbits (3 to 50 mg/kg/day), and monkeys (1 to 3 mg/kg/day) before and during gestation, no teratogenic effects were seen. (See Precautions.)

Usage in Children—The use of Navane in children under 12 years of age is not recommended because safety and efficacy in the pediatric age group have not been established.

As is true with many CNS drugs, Navane may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery, especially during the first few days of therapy. Therefore, the patient should be cautioned accordingly.

As in the case of other CNS-acting drugs, patients receiving Navane should be cautioned about the possible additive effects (which may include hypotension) with CNS depressants and with alcohol.

Precautions: An antiemetic effect was observed in animal studies with Navane; since this effect may also occur in man, it is possible that Navane may mask signs of overdosage of toxic drugs and may obscure conditions such as intestinal obstruction and brain tumor.

In consideration of the known capability of Navane and certain other psychotropic drugs to precipitate convulsions, extreme caution should be used in patients with a history of convulsive disorders or those in a state of alcohol withdrawal since it may lower the convulsive threshold. Although Navane potentiates the actions of the barbiturates, the dosage of the anticonvulsant therapy should not be reduced when Navane is administered concurrently.

Caution as well as careful adjustment of the dosage is indicated when Navane is used in conjunction with other CNS depressants other than anticonvulsant drugs.

Though exhibiting rather weak anticholinergic properties, Navane should be used with caution in patients who are known or suspected to have glaucoma, or who might be exposed to extreme heat, or who are receiving atropine or related drugs.

Use with caution in patients with cardiovascular disease.

Also, careful observation should be made for pigmentary retinopathy, and lenticular pigmentation (fine lenticular pigmentation has been noted in a small number of patients treated with Navane for prolonged periods). Blood dyscrasias (agranulocytosis, pancytopenia, thrombocytopenic purpura), and liver damage (jaundice, biliary stasis) have been reported with related drugs.

Undue exposure to sunlight should be avoided. Photosensitive reactions have been reported in patients on Navane.

Neuroleptic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of neuroleptic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time.

Intramuscular Administration—As with all intramuscular preparations, Navane intramuscular should be injected well within the body of a relatively large muscle. The preferred sites are the upper outer quadrant of the buttock (i.e. gluteus maximus) and the mid-lateral thigh.

The deltoid area should be used only if well developed, such as in certain adults and older children, and then only with caution to avoid radial nerve injury. Intramuscular injections should not be made into the lower and mid-thirds of the upper arm. As with all intramuscular injections, aspiration is necessary to help avoid inadvertent injection into a blood vessel.

Adverse Reactions: Note: Not all of the following adverse reactions have been reported with Navane (thiothixene). However, since Navane has certain chemical and pharmacologic similarities to the phenothiazines, all of the known side effects and toxicity associated with phenothiazine therapy should be borne in mind when Navane is used.

Cardiovascular effects: Tachycardia, hypotension, lightheadedness, and syncope. In the event hypotension occurs, epinephrine should not be used as a pressor agent since a paradoxical further lowering of blood pressure may result. Nonspecific EKG changes have been observed in some patients receiving Navane (thiothixene). These changes are usually reversible and frequently disappear on continued Navane therapy. The incidence of these changes is lower than that observed with some phenothiazines. The clinical significance of these changes is not known.

CNS effects: Drowsiness, usually mild, may occur although it usually subsides with continuation of Navane therapy. The incidence of sedation appears similar to that of the piperazine group of phenothiazines, but less than that of certain aliphatic phenothiazines. Restlessness, agitation and insomnia have been noted with Navane. Seizures and paradoxical exacerbation of psychotic symptoms have occurred with Navane infrequently. Hyperreflexia has been reported in infants delivered from mothers having received structurally related drugs.

In addition, phenothiazine derivatives have been associated with cerebral edema and cerebrospinal fluid abnormalities.

Extrapyramidal symptoms, such as pseudo-parkinsonism, akathisia, and dystonia have been reported. Management of these extrapyramidal symptoms depends upon the type and severity. Rapid relief of acute symptoms may require the use of an injectable antiparkinson agent. More slowly emerging symptoms may be managed by reducing the dosage of Navane and/or administering an oral antiparkinson agent.

Persistent Tardive Dyskinesia: As with all antipsychotic agents tardive dyskinesia may appear in some patients on long term therapy or may occur after drug therapy has been discontinued. The risk seems to be greater in elderly patients on high-dose therapy, especially females. The symptoms are persistent and in some patients appear to be irreversible. The syndrome is characterized by rhythmic involuntary movements of the tongue, face, mouth or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities.

Since early detection of tardive dyskinesia is important, patients should be monitored on an ongoing basis. It has been reported that fine vermicular movement of the tongue may be an early sign of the syndrome. If any or other presentation of the syndrome is observed, the clinician should consider possible discontinuation of neuroleptic medication. (See Warnings section.)

Hepatic Effects: Elevations of serum transaminase and alkaline phosphatase, usually transient, have been infrequently observed in some patients. No clinically confirmed cases of jaundice attributable to Navane have been reported.

Hematologic Effects: As is true with certain other psychotropic drugs, leukopenia and leukocytosis, which are usually transient, can occur occasionally with Navane. Other antipsychotic drugs have been associated with agranulocytosis, eosinophilia, hemolytic anemia, thrombocytopenia and pancytopenia.

Allergic Reactions: Rash, pruritus, urticaria, photosensitivity and rare cases of anaphylaxis have been reported with Navane. Undue exposure to sunlight should be avoided. Although not experienced with Navane, exfoliative dermatitis and contact dermatitis (in nursing personnel) have been reported with certain phenothiazines.

Endocrine Disorders: Lactation, moderate breast enlargement and amenorrhea have occurred in a small percentage of females receiving Navane. If persistent, this may necessitate a reduction in dosage or the discontinuation of therapy. Phenothiazines have been associated with false positive pregnancy tests, gynecomastia, hypoglycemia, hyperglycemia, and glycosuria.

Autonomic Effects: Dry mouth, blurred vision, nasal congestion, constipation, increased sweating, increased salivation, and impotence have occurred infrequently with Navane therapy. Phenothiazines have been associated with miosis, mydriasis, and adynamic ileus.

Other Adverse Reactions: Hyperpyrexia, anorexia, nausea, vomiting, diarrhea, increase in appetite and weight, weakness or fatigue, polydipsia and peripheral edema.

Although not reported with Navane, evidence indicates there is a relationship between phenothiazine therapy and the occurrence of a systemic lupus erythematosus-like syndrome.

NOTE: Sudden deaths have occasionally been reported in patients who have received certain phenothiazine derivatives. In some cases the cause of death was apparently cardiac arrest or asphyxia due to failure of the cough reflex. In others, the cause could not be determined nor could it be established that death was due to phenothiazine administration.

Dosage and Administration: Dosage of Navane should be individually adjusted depending on the chronicity and severity of the condition. In general, small doses should be used initially and gradually increased to the optimal effective level, based on patient response.

Some patients have been successfully maintained on once-a-day Navane therapy.

Usage in children under 12 years of age is not recommended because safe conditions for its use have not been established.

Navane Intramuscular Solution: Navane For Injection—When more rapid control and treatment of acute behavior is desirable, the intramuscular form of Navane may be indicated. It is also of benefit where the very nature of the patient's symptomatology, whether acute or chronic, renders oral administration impractical or even impossible.

For treatment of acute symptomatology or in patients unable or unwilling to take oral medication, the usual dose is 4 mg of Navane intramuscular administered 2 to 4 times daily. Dosage may be increased or decreased depending on response. Most patients are controlled on a total daily dosage of 16 to 20 mg. The maximum recommended dosage is 30 mg/day. An oral form should supplant the injectable form as soon as possible. It may be necessary to adjust the dosage when changing from the intramuscular to oral dosage forms. Dosage recommendations for Navane (thiothixene) Capsules and Concentrate appear in the following paragraphs.

Navane Capsules: Navane Concentrate—In milder conditions, an initial dose of 2 mg three times daily. If indicated, a subsequent increase to 15 mg/day total daily dose is often effective.

In more severe conditions, an initial dose of 5 mg twice daily.

The usual optimal dose is 20 to 30 mg daily. If indicated, an increase to 60 mg/day total daily dose is often effective. Exceeding a total daily dose of 60 mg rarely increases the beneficial response.

Overdosage: Manifestations include muscular twitching, drowsiness, and dizziness. Symptoms of gross overdosage may include CNS depression, rigidity, weakness, torticollis, tremor, salivation, dysphagia, hypotension, disturbances of gait, or coma.

Treatment: Essentially is symptomatic and supportive. For Navane oral, early gastric lavage is helpful. For Navane oral and intramuscular, keep patient under careful observation and maintain an open airway, since involvement of the extrapyramidal system may produce dysphagia and respiratory difficulty in severe overdosage. If hypotension occurs, the standard measures for managing circulatory shock should be used (I.V. fluids and/or vasoconstrictors.)

If a vasoconstrictor is needed, levaterenol and phenylephrine are the most suitable drugs. Other pressor agents, including epinephrine, are not recommended, since phenothiazine derivatives may reverse the usual pressor action of these agents and cause further lowering of the blood pressure.

If CNS depression is present and specific therapy is indicated, recommended stimulants include amphetamine, dextroamphetamine, or caffeine and sodium benzoate. Stimulants that may cause convulsions (e.g. picrotoxin or penitlenetrazol) should be avoided. Extrapyramidal symptoms may be treated with antiparkinson drugs.

There are no data on the use of peritoneal or hemodialysis, but they are known to be of little value in phenothiazine intoxication.

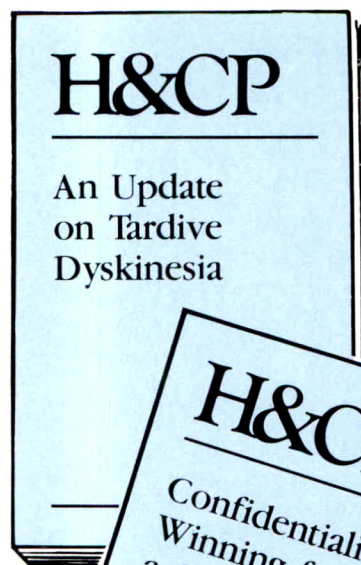
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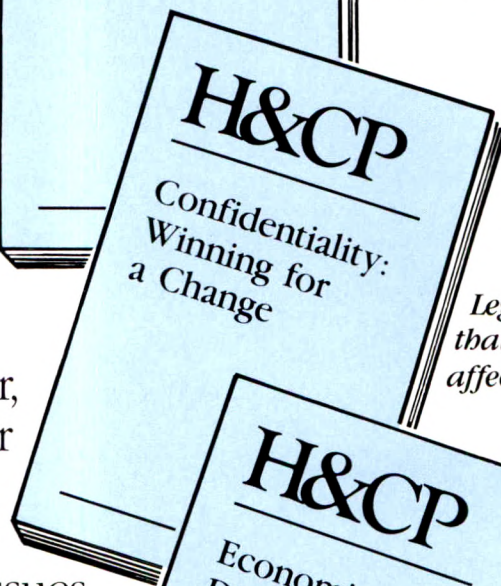
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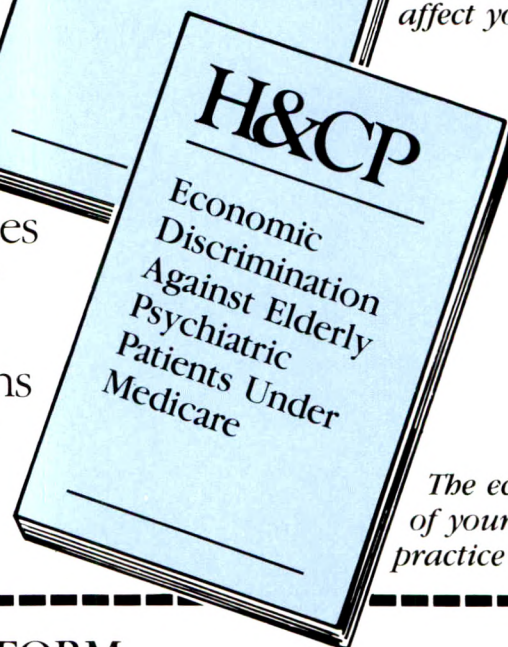
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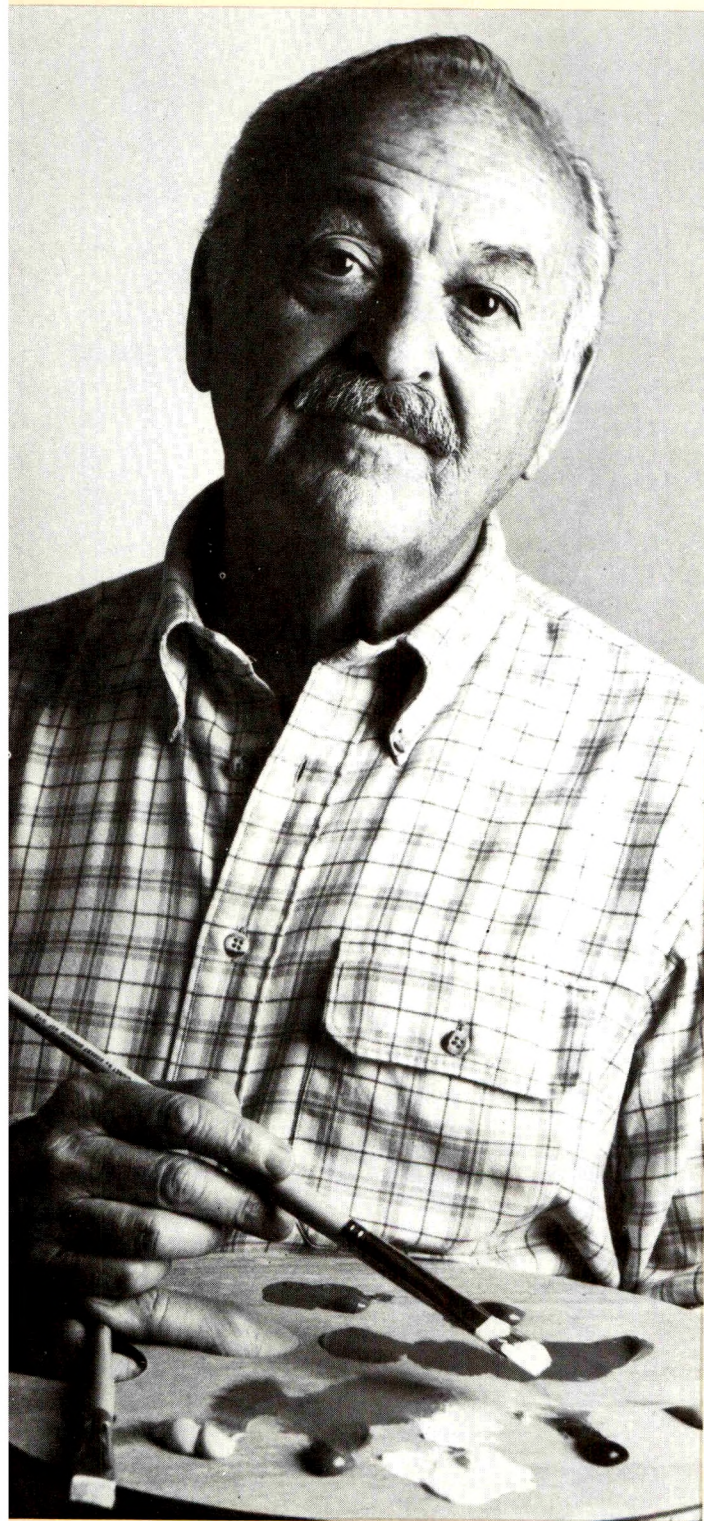
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WARNINGS: Tardive Dyskinesia—This syndrome (potentially irreversible, involuntary, dyskinetic movements) may develop in patients treated with neuroleptic (antipsychotic) drugs. Prevalence appears highest among the elderly, especially women; it is impossible to predict which patients are likely to develop the syndrome. Both risk of syndrome development and likelihood of its becoming irreversible are believed to increase with duration of treatment and total cumulative dose; the syndrome can develop after brief treatment periods at low doses. There is no known treatment; partial or complete remission may occur if neuroleptic treatment is withdrawn. Neuroleptic treatment may suppress or partially suppress signs and symptoms of the syndrome and thereby mask the underlying disease process. Effect of symptomatic suppression upon long-term course of the syndrome is unknown. Prescribe neuroleptics in a manner most likely to minimize the occurrence of tardive dyskinesia. Reserve chronic neuroleptic treatment for patients suffering from a chronic illness that is known to respond to neuroleptic drugs and for whom alternative treatments are not available or appropriate. In those requiring chronic treatment the smallest dose and shortest duration of treatment producing satisfactory clinical response should be sought. Need for treatment should be reassessed periodically. Consider discontinuing treatment if signs and symptoms of tardive dyskinesia appear; some patients may require treatment despite presence of the syndrome.

Usage in Pregnancy: Studies in pregnant patients have not been carried out. Animal reproductive studies have not demonstrated a teratogenic potential. Anticipated benefits must be weighed against the unknown risks to the fetus if used in pregnant patients.

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Usage in Children: Use of MOBAN in children below the age of twelve years is not recommended because safe and effective conditions for its usage have not been established. MOBAN has not been shown effective in the management of behavioral complications in patients with mental retardation.

Sulfites Sensitivity: MOBAN Concentrate contains sodium metabisulfite, a sulfite that may cause allergic-type reactions (e.g., hives, itching, wheezing, anaphylaxis) in certain susceptible persons. Although the overall prevalence of sulfite sensitivity in the general population is probably low, it is seen more frequently in asthmatics or in atopic nonasthmatic persons.

PRECAUTIONS: Some patients may note drowsiness initially; advise against activities requiring mental alertness until response to the drug has been established. Increased activity has been noted in patients receiving MOBAN. Caution should be exercised where increased activity may be harmful. MOBAN does not lower the seizure threshold in experimental animals to the degree noted with more sedating antipsychotic drugs; in humans convulsive seizures have been reported in a few instances. This tablet preparation contains calcium sulfate as an excipient; calcium ions may interfere with the absorption of preparations containing phenytoin sodium and tetracyclines. MOBAN has an antiemetic effect in animals. A similar effect may occur in humans and may obscure signs of intestinal obstruction or brain tumor. Neuroleptic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent in vitro, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time.

ADVERSE REACTIONS: CNS EFFECTS: Most frequently occurring effect is initial drowsiness that generally subsides with continued usage or lowering of the dose. Noted less frequently were depression, hyperactivity and euphoria.

Neurological—Extrapyramidal Reactions noted below may occur in susceptible individuals; usually reversible with appropriate management.

Akathisia: Motor restlessness may occur early.

Parkinson Syndrome: Akinesia, characterized by rigidity, immobility and reduction of voluntary movements and tremor, have been observed. Occurrence is less frequent than akathisia.

Dystonic Syndrome: Prolonged abnormal contractions of muscle groups occur infrequently. Symptoms may be managed by the addition of a synthetic antiparkinson agent (other than L-dopa), small doses of sedative drugs, and/or reduction in dosage.

Tardive Dyskinesia: Persistent and sometimes irreversible. See preceding paragraph under "Warnings."

Autonomic Nervous System: Occasional blurring of vision, tachycardia, nausea, dry mouth and salivation. Urinary retention and constipation may occur, particularly if anticholinergic drugs are used to treat extrapyramidal symptoms.

Laboratory Tests: Rare reports of leucopenia and leucocytosis; treatment with MOBAN may continue if clinical symptoms are absent. Alterations of blood glucose, liver function tests, BUN, and red blood cells have not been considered clinically significant.

Metabolic and Endocrine Effects: Alteration of thyroid function has not been significant. Amenorrhea has been reported infrequently. Resumption of menses in previously amenorrheic women has been reported. Initially heavy menses may occur. Galactorrhea and gynecomastia have been reported infrequently. Increase in libido has been noted in some patients. Impotence has not been reported. Although both weight gain and weight loss have been in the direction of normal or ideal weight, excessive weight gain has not occurred with MOBAN.

Hepatic Effects: There have been rare reports of clinically significant alterations in liver function in association with MOBAN use.

Cardiovascular: Rare, transient, non-specific T wave changes have been reported on EKG. Association with a clinical syndrome has not been established. Rarely has significant hypotension been reported.

Ophthalmological: Lens opacities and pigmentary retinopathy have not been reported. In some patients phenothiazine-induced lenticular opacities have resolved following discontinuation of the phenothiazine while continuing therapy with MOBAN.

Skin: Early non-specific skin rash, probably of allergic origin, has occasionally been reported. Skin pigmentation has not been seen with MOBAN usage alone. MOBAN has certain pharmacological similarities to other antipsychotic agents. Because adverse reactions are often extensions of the pharmacological activity of a drug, all of the known pharmacological effects associated with other antipsychotic drugs should be kept in mind when MOBAN is used. Upon abrupt withdrawal after prolonged high dosage an abstinence syndrome has not been noted.

DOSAGE: Initial and maintenance doses of MOBAN should be individualized. See full prescribing information.

OVERDOSAGE: For information on signs and symptoms, and treatment of overdosage, see full prescribing information.

HOW SUPPLIED: Tablets: 5 mg, 10 mg, 25 mg, 50 mg and 100 mg in bottles of 100.

Concentrate: 20 mg/ml in 4 oz (120 ml) bottles.

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BRIEF SUMMARY

ASENDIN® amoxapine Tablets
25 mg, 50 mg, 100 mg, 150 mg

CLINICAL PHARMACOLOGY: ASENDIN is an antidepressant with a mild sedative component to its action. The mechanism of its clinical action in man is not well understood. In animals, amoxapine reduced the uptake of norepinephrine and serotonin and blocked the response of dopamine receptors to dopamine. Amoxapine is not a monoamine oxidase inhibitor.

ASENDIN is absorbed rapidly and reaches peak blood levels approximately 90 minutes after ingestion. It is almost completely metabolized. The main route of excretion is the kidney. In vitro tests show that amoxapine binding to human serum is approximately 90%. In man, amoxapine serum concentration declines with a half-life of eight hours. However, the major metabolite, 8-hydroxyamoxapine, has a biologic half-life of 30 hours. Metabolites are excreted in the urine in conjugated form as glucuronides.

Clinical studies have demonstrated that ASENDIN has a more rapid onset of action than either amitriptyline or imipramine. The initial clinical effect may occur within four to seven days and occurs within 2 weeks in over 80% of responders.

INDICATIONS: ASENDIN is indicated for relief of symptoms of depression in patients with neurotic or reactive depressive disorders as well as endogenous and psychotic depressions and depression accompanied by anxiety or agitation.

CONTRAINDICATIONS: Prior hypersensitivity to dibenzoxazine compounds and in the acute recovery phase following myocardial infarction. Do not give concomitantly with monoamine oxidase inhibitors. Hyperpyretic crises, severe convulsions, and deaths have occurred in patients receiving tricyclic antidepressants and monoamine oxidase inhibitors simultaneously. Before replacing a monoamine oxidase inhibitor with ASENDIN® amoxapine, allow a minimum of 14 days to elapse, then initiate cautiously with gradual increase in dosage until optimum response is achieved.

WARNINGS: Tardive Dyskinesia: Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may develop in patients treated with neuroleptic (ie, antipsychotic) drugs. (Amoxapine is not an antipsychotic, but it has substantial neuroleptic activity.) Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of neuroleptic treatment, which patients are likely to develop the syndrome. Whether neuroleptic drug products differ in their potential to cause tardive dyskinesia is unknown.

Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dosage of neuroleptic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if neuroleptic treatment is withdrawn. Neuroleptic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying disease process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, neuroleptics should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic neuroleptic treatment should generally be reserved for patients who suffer from a chronic illness that (1) is known to respond to neuroleptic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on neuroleptics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome.

(For further information about the description of tardive dyskinesia and its clinical detection, please refer to the sections on Information for Patients and Adverse Reactions.)

Use with caution in patients with history of urinary retention, angle-closure glaucoma, or increased intraocular pressure. Watch patients with cardiovascular disorders closely. Tricyclic antidepressants, particularly in high doses, can induce sinus tachycardia, changes in conduction time, and arrhythmias. Myocardial infarction and stroke have been reported with drugs of this class. Take extreme caution in patients with history of convulsive disorders or those with overt or latent seizure disorders.

PRECAUTIONS: General: Because of inherent suicide potential, dispense to severely depressed patients the smallest suitable amount of the drug. Manic depressive patients may experience a shift to the manic phase; schizophrenic patients may develop increased symptoms of psychosis; patients with paranoid symptomatology may have such symptoms exaggerated, requiring reduction of dosage or addition of a major tranquilizer to the therapeutic regimen. Antidepressant drugs can cause skin rashes and/or "drug fever" in susceptible individuals. These allergic reactions may, in rare cases, be severe. They are more likely to occur during the first few days of treatment, but may also occur later. ASENDIN® amoxapine should be discontinued if rash and/or fever develop. Amoxapine possesses a degree of dopamine-blocking activity which may cause extrapyramidal symptoms in <1% of patients. Rarely, symptoms indicative of tardive dyskinesia have been reported. Information for the patient: It is advised that all patients in whom chronic use of neuroleptic drugs is contemplated be given full information about the risk of tardive dyskinesia. Warn patients of possibility of drowsiness; performance of potentially hazardous tasks such as driving an automobile or operating machinery may be impaired. Drug interactions: See Contraindications regarding concurrent usage of tricyclic antidepressants and monoamine oxidase inhibitors. Paralytic ileus may occur when tricyclic antidepressants are taken in combination with anticholinergic drugs. ASENDIN may enhance response to alcohol and the effects of barbiturates and other CNS depressants. Serum levels of several tricyclic antidepressants have been reported to be significantly increased when cimetidine is administered concurrently. Although such an interaction has not been reported to date with ASENDIN, specific interaction studies have not been done, and the possibility should be considered. Therapeutic interactions: Concurrent administration with electroshock may increase hazards associated with such therapy. Carcinogenesis, impairment of fertility: In a 21-month toxicity study at three-dose levels in rats, pancreatic islet cell hyperplasia occurred with slightly increased incidence at doses 5-10 times the human dose. Pancreatic adenocarcinoma was detected in low incidence in the mid-dose group only, and may possibly have resulted from endocrine-mediated organ hyperfunction. The significance of these findings to man is not known. Treatment of male rats with 5-10 times the human dose resulted in a slight decrease in the number of fertile matings. Female rats receiving oral doses within the therapeutic range displayed a reversible increase in estrous cycle length. Pregnancy: Pregnancy Category C: Studies performed in mice, rats, and rabbits have demonstrated no evidence of teratogenic effect due to ASENDIN. Embryotoxicity was seen in rats and rabbits given oral doses approximating the human dose. Fetotoxic effects (intrauterine death, stillbirth, decreased birth weight) were seen in animals studied at oral doses 3-10 times the human dose. Decreased postnatal survival (between days 0-4) was demonstrated in the offspring of rats at 5-10 times the human dose. There are no adequate and well-controlled studies of pregnant women. ASENDIN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Nursing mothers: ASENDIN, like many other systemic drugs, is excreted in human milk. Because effects of the drug on infants are unknown, caution should be exercised when ASENDIN is administered to nursing women. Pediatric use: Safety and effectiveness in children below the age of 16 have not been established.

ADVERSE REACTIONS: Reported in Controlled Studies: Incidence greater than 1%—Most frequent were sedative and anticholinergic—drowsiness (14%), dry mouth (14%), constipation (12%), and blurred vision (7%).

Less frequently reported reactions were: CNS and Neuromuscular—anxiety, insomnia, restlessness, nervousness, palpitations, tremors, confusion, excitement, nightmares, ataxia, alterations in EEG patterns. Allergic—edema, skin rash. Endocrine—elevation of prolactin levels. Gastrointestinal—nausea. Other—dizziness, headache, fatigue, weakness, excessive appetite, increased perspiration. Incidence less than 1%—Anticholinergic—disturbances of accommodation, mydriasis, delayed micturition, urinary retention, nasal stuffiness. Cardiovascular—hypotension, hypertension, syncope, tachycardia. Allergic—drug fever, urticaria, photosensitization, pruritus, rarely, vasculitis, hepatitis. CNS and Neuromuscular—tingling, paresthesias of the extremities, linitis, disorientation, seizures, hypomania, numbness, incoordination, disturbed concentration, hyperthermia, extrapyramidal symptoms, including, rarely, tardive dyskinesia. Neuroleptic malignant syndrome has been reported. Hematologic—leukopenia, agranulocytosis. Gastrointestinal—epigastric distress, vomiting, flatulence, abdominal pain, peculiar taste, diarrhea. Endocrine—increased or decreased libido, impotence, menstrual irregularity, breast enlargement, and galactorrhea in the female, syndrome of inappropriate antidiuretic hormone secretion. Other—lactation, weight gain or loss, altered liver function. Drug Relationship Unknown: Reported rarely, but under circumstances where drug relationship was unknown: Anticholinergic—paralytic ileus. Cardiovascular—atrial arrhythmias (including atrial fibrillation), myocardial infarction, stroke, heart block. CNS and Neuromuscular—hallucinations. Hematologic—thrombocytopenia, eosinophilia, purpura, ptelechiae. Gastrointestinal—parotid swelling. Endocrine—change in blood glucose levels. Other—pancreatitis, hepatitis, jaundice, urinary frequency, testicular swelling, anorexia, alopecia.

Additional Adverse Reactions Reported with Other Antidepressant Drugs: Anticholinergic—sublingual adenitis, dilation of the urinary tract. CNS and Neuromuscular—delusions. Gastrointestinal—stomatitis, black tongue. Endocrine—gynecomastia.

OVERDOSAGE: Signs and Symptoms

Toxic manifestations of ASENDIN® amoxapine overdosage differ significantly from those of other tricyclic antidepressants. Serious cardiovascular effects are seldom, if ever, observed. However, CNS effects—particularly grand mal convulsions—occur frequently, and treatment should be directed primarily toward prevention or control of seizures. Status epilepticus may develop and constitutes a neurologic emergency. Coma and acidosis are other serious complications of substantial ASENDIN overdosage in some cases. Renal failure may develop two to five days after toxic dosage, typically in those who have experienced multiple seizures.

Treatment

Treatment of ASENDIN overdosage should be symptomatic and supportive, but with special attention to prevention or control of seizures. Seizures may respond to standard anticonvulsive therapies, such as intravenous diazepam and/or phenytoin. The value of physostigmine appears less certain. Status epilepticus, should it develop, requires vigorous treatment such as that described by Delgado-Escueta, et al. (N Engl J Med 1982; 306: 1337-1340).

Convulsions, when they occur, typically begin within 12 hours after ingestion. Prophylactic administration of anticonvulsant medication during this period may be of value. Treatment of renal failure, should it occur, is the same as that for non-drug-induced renal dysfunction. Serious cardiovascular effects are remarkably rare following ASENDIN overdosage, and the ECG typically remains within normal limits, except for sinus tachycardia. Hence, prolongation of the QRS interval beyond 100 milliseconds within the first 24 hours is not a useful guide to the severity of overdosage with this drug. Fatalities and, rarely, neurologic sequelae have resulted from prolonged status epilepticus in ASENDIN overdosage patients.

Rev. 12/85

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1. Hekiman LJ, Friedhoff AJ, Deever E: A comparison of the onset of action and therapeutic efficacy of amoxapine and amitriptyline. J Clin Psychiatry 1978;39:633-637.
2. Data on file, Lederle Laboratories, Pearl River, N.Y.
3. Hekiman LJ, Weise CC, Friedhoff AJ: Onset of action of amoxapine and doxepin in outpatients with "mixed anxiety depression." J Clin Psychiatry 1983; 44:248-252.
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5. Fabre LF: The treatment of depression in outpatients: A controlled comparison of the onset of action of amoxapine and maprotiline. J Clin Psychiatry, 1985;46:521-524.

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Calendar

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APRIL

April 1-5, The Future of Adult Life: 1st International Conference, the Netherlands. Contact Conference Secretariat, c/o CONGREX, Keizersgracht 610, 1017 EP Amsterdam, the Netherlands; 3120-270401; Telex 14527 CONGRX.

April 2-5, annual meeting, American College of Physicians, New Orleans. Contact John Ball, M.D., Executive Vice-President, 4200 Pine St., Philadelphia, PA 19104; 215-243-1200.

April 5-8, annual meeting, American Occupational Therapy Association, Indianapolis. Contact James J. Garibaldi, Executive Director, 1383 Piccard Dr., Suite 300, Rockville, MD 20850; 301-948-9626.

April 5-9, International Conference on New Directions in Affective Disorders, Jerusalem. Contact Conference Secretariat, International Ltd., New Directions in Affective Disorders, 12 Shlomzion Hamalka St., Jerusalem 94 146 Israel.

April 5-11, annual meeting, American Academy of Neurology, New York. Contact Jan W. Kolehmainen, Executive Director, 2221 University Ave., S.E., Suite 335, Minneapolis, MN 55414; 612-623-8115.

April 6-11, annual meeting, American Society of Clinical Hypnosis, Las Vegas. Contact William F. Hoffmann, Jr., Executive Vice-President, 2250 East Devon Ave., Suite 336, Des Plaines, IL 60018; 312-297-3317.

April 9-11, semiannual meeting, Group for the Advancement of Psychiatry, White Plains, N.Y. Contact Michael R. Zales, M.D., President, P.O. Box 330, Greenbelt, MD 20770; 301-345-8030.

April 15-20, Sixth International Conference, Adolescents in Crisis, Barbados, West Indies. Contact Pamela McMahon, Southern California Neuropsychiatric Institute, 6794 La Jolla Blvd., La Jolla, CA 92037; 619-454-2102.

April 17-18, annual meeting, Bulimia Anorexia Self-Help, Inc., St. Louis. Contact Felix E.F. Larocca, M.D., Executive Director, 6125 Clayton Ave., Suite 215, St. Louis, MO 63139; 314-567-4080.

April 22-24, 28th National Student Research Forum, University of Texas Medical Branch, Galveston, Tex. Contact National Student Research Forum, UTMB, P.O. Box 54—Station 1, Galveston, TX 77550; 409-761-3762.

April 22-25, annual meeting, American Association for Counseling and Development, New Orleans. Contact Patrick J. McDonough, Ed.D., Executive Director, 5999 Stevenson Ave., Alexandria, VA 22304; 703-823-9800.

April 22-25, Fifth Annual Symposium in Psychiatry and Law, American College of Forensic Psychiatry, Monterey, Calif. Contact Ed Miller, Executive Director, 26701 Quail Creek, Suite 295, Laguna Hills, CA 92656; 714-831-0236.

April 22-27, annual meeting, National Council on Alcoholism, Inc., Cleveland. Contact Thomas V. Seesel, Executive Director, 12 West 21st St., 7th Fl., New York, NY 10010; 212-206-6770.

April 23-26, annual conference, American Medical Society on Alcoholism and Other Drug Dependencies, Cleveland. Contact Claire Osman, AMSAODD Administrative Director, 12 West 21st St., New York, NY 10010; 212-206-6770.

April 26-28, part II examinations, American Board of Psychiatry and Neurology, Los Angeles. Contact Stephen C. Scheiber, M.D., Executive Secretary, Suite 808, 1 American Plaza, Evanston, IL 60201; 312-864-0830.

April 26-May 1, annual meeting, American Occupational Medical Association, Philadelphia. Contact Donald L. Hoops, Ph.D., Executive Director, 2340 S. Arlington Hgts. Rd., Suite 400, Arlington Heights, IL 60005; 312-228-6850.

April 27-May 1, annual meeting, American Pediatric Society, Anaheim, Calif. Contact Audrey Brown, M.D., Secretary, Dept. of Pediatrics, Box 49, Downstate Medical Center, 450 Clarkson Ave., Brooklyn, NY 11203; 718-270-1692.

April 29-May 2, annual meeting, American Association for the History of Medicine, Inc., Philadelphia. Contact Edward C. Atwater, M.D., Secretary-Treasurer, University of Rochester Medical Center, 601 Elmwood Ave., Rochester, NY 14642; 716-275-2903.

April 29-May 3, annual meeting, American Association of Pastoral Counselors, New Orleans. Contact James W. Ewing, Ph.D., Executive Director, 9508 A Lee Hwy., Fairfax, VA 22031; 703-385-6967.

MAY

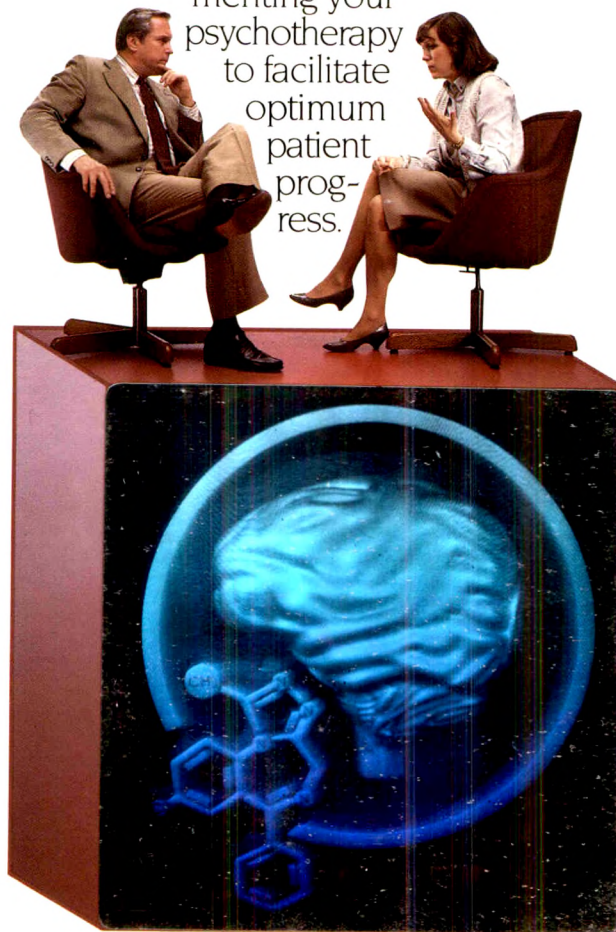
May 1-4, annual meeting, American Federation for Clinical Research, Eastern Section, San Diego. Contact Robert K.

(Continued on page A30)

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Xanax effectively relieves anxiety associated with depression, complementing your psychotherapy to facilitate optimum patient progress.



Xanax[®] 0.5 mg
Tablets
alprazolam[®]

**COMPLEMENTS AN EFFECTIVE
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Xanax[®] 0.5 mg
alprazolam ^{IV} Tablets

XANAX[®] Tablets (alprazolam) ©

CONTRAINDICATIONS

Patients with sensitivity to this drug or other benzodiazepines and in acute narrow angle glaucoma.

WARNINGS

Not of value in psychotic patients. Caution patients against hazardous occupations requiring complete mental alertness and about the simultaneous ingestion of alcohol and other CNS depressant drugs.

Benzodiazepines can cause fetal harm in pregnant women. Warn patients of the potential hazard to the fetus. Avoid during the first trimester.

PRECAUTIONS

General: The dosage of XANAX Tablets should be reduced or withdrawn gradually, since withdrawal seizures have been reported upon abrupt withdrawal. If XANAX is combined with other psychotropics or anticonvulsant drugs, consider drug potentiation (see Drug Interaction section). Exercise the usual precautions regarding size of the prescription for depressed or suicidal patients. In elderly and debilitated patients, use the lowest possible dosage (see Dosage and Administration). Observe the usual precautions in treating patients with impaired renal or hepatic function.

Information for Patients: Alert patients about: (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing dose of the drug due to risk of dependence, (e) not stopping the drug abruptly. **Laboratory Tests:** Not ordinarily required in otherwise healthy patients. **Drug Interactions:** Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistamines, ethanol and other CNS depressants. Pharmacokinetic interactions with ben-

zodiazepines have been reported. **Drug/Laboratory Test Interactions:** No consistent pattern for a specific drug or specific test. **Carcinogenesis, Mutagenesis, Impairment of Fertility:** No carcinogenic potential or impairment of fertility in rats. **Pregnancy:** See Warnings. **Nonteratogenic Effects:** The child born of a mother on benzodiazepines may be at some risk for withdrawal symptoms and neonatal flaccidity. **Labor and Delivery:** No established use. **Nursing Mothers:** Benzodiazepines are excreted in human milk. Women on XANAX should not nurse. **Pediatric Use:** Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS

Side effects are generally observed at the beginning of therapy and usually disappear with continued medication. In the usual patient, the most frequent side effects are likely to be an extension of the pharmacologic activity of XANAX, eg, drowsiness or lightheadedness.

Central nervous system: Drowsiness, lightheadedness, depression, headache, confusion, insomnia, nervousness, syncope, dizziness, akathisia, and tiredness/sleepiness.

Gastrointestinal: Dry mouth, constipation, diarrhea, nausea/vomiting, and increased salivation.

Cardiovascular: Tachycardia/palpitations, and hypotension.

Sensory: Blurred vision.

Musculoskeletal: Rigidity and tremor.

Cutaneous: Dermatitis/allergy.

Other side effects: Nasal congestion, weight gain, and weight loss.

In addition, the following adverse events have been reported with the use of benzodiazepines: dystonia, irritability, concentration difficulties, anorexia, transient amnesia or memory impairment, loss of coordination, fatigue, sedation, slurred speech, jaundice, musculoskeletal weakness, pruritus, diplopia,

dysarthria, changes in libido, menstrual irregularities, incontinence and urinary retention.

Paradoxical reactions such as stimulation, agitation, increased muscle spasticity, sleep disturbances, and hallucinations may occur. Should these occur, discontinue the drug.

During prolonged treatment, periodic blood counts, urinalysis, and blood chemistry analysis are advisable. Minor EEG changes of unknown significance have been observed.

DRUG ABUSE AND DEPENDENCE

Physical and Psychological Dependence: Withdrawal symptoms have occurred following abrupt discontinuance of benzodiazepines. Withdrawal seizures have occurred upon rapid decrease or abrupt discontinuation of therapy. In all patients, dosage should be gradually tapered under close supervision. Patients with a history of seizures or epilepsy should not be abruptly withdrawn from XANAX. Addiction-prone individuals should be under careful surveillance. **Controlled Substance Class:** XANAX is a controlled substance and has been assigned to schedule IV.

CAUTION: FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION.

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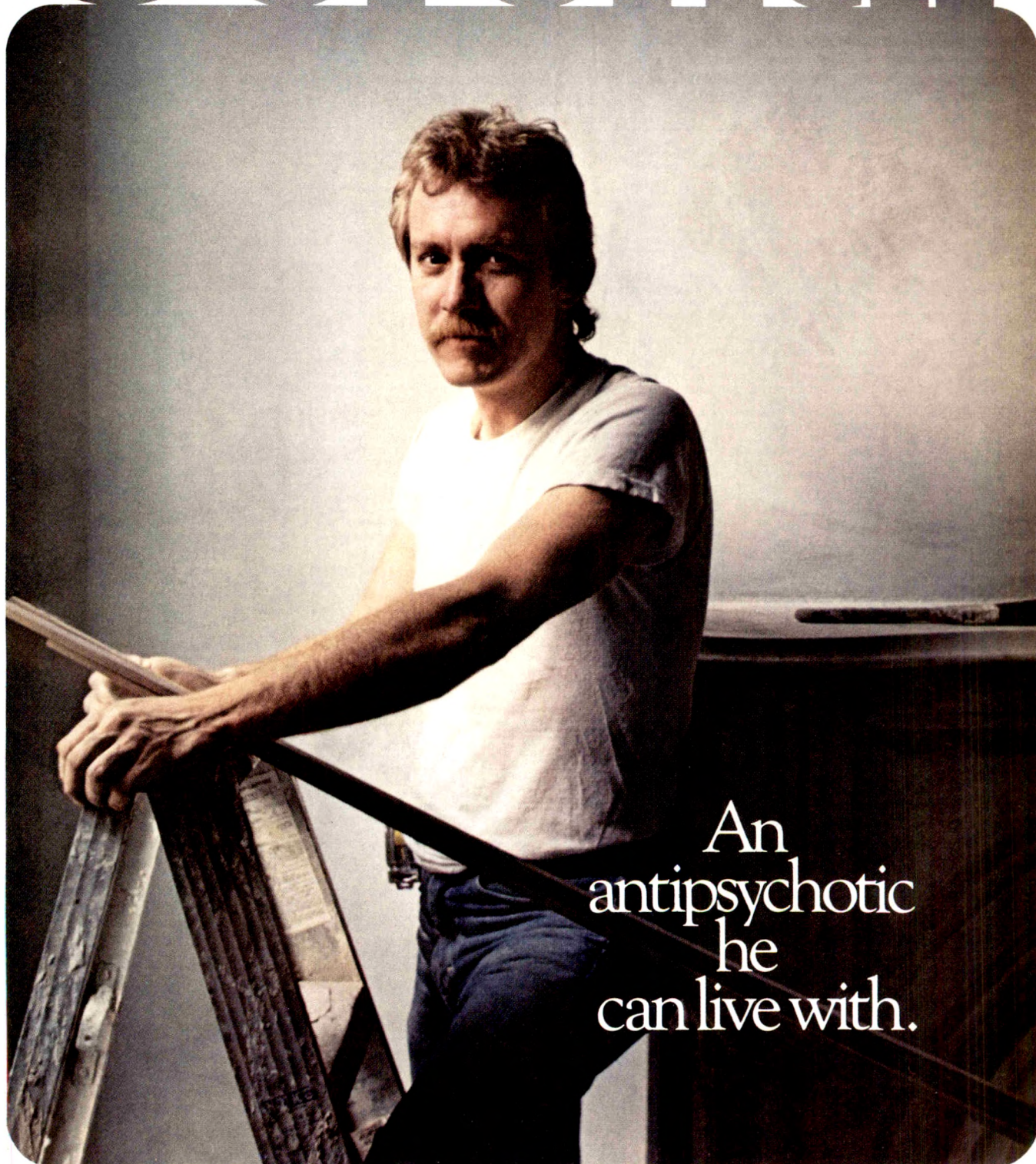
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(mesoridazine) as the besylate
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Sereniti



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Please see following page for brief summary of prescribing information.

Sereniti[®] (mesoridazine) as the besylate

(mesoridazine) besylate tablets USP
(mesoridazine) besylate injection USP
(mesoridazine) besylate oral solution USP



Tablets: 10, 25, 50 and 100 mg



Concentrate: 25 mg/ml



Injectable: 1 ml (25 mg)

Brief Summary of Prescribing Information

Contraindications: As with other phenothiazines, Sereniti[®] (mesoridazine), is contraindicated in severe central nervous system depression or comatose states from any cause. Sereniti is contraindicated in individuals who have previously shown hypersensitivity to the drug.

Warnings: *Tardive Dyskinesia:* Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with neuroleptic (antipsychotic) drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of neuroleptic treatment, which patients are likely to develop the syndrome. Whether neuroleptic drug products differ in their potential to cause tardive dyskinesia is unknown.

Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of neuroleptic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if neuroleptic treatment is withdrawn. Neuroleptic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying disease process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, neuroleptics should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic neuroleptic treatment should generally be reserved for patients who suffer from a chronic illness 1) that is known to respond to neuroleptic drugs, and 2) for which alternative, equally effective but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on neuroleptics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome.

(For further information about the description of tardive dyskinesia and its clinical detection, please refer to the sections on Information for Patients and Adverse Reactions.) Where patients are participating in activities requiring complete mental alertness (e.g., driving) it is advisable to administer the phenothiazines cautiously and to increase the dosage gradually.

Usage in Pregnancy: The safety of this drug in pregnancy has not been established; hence, it should be given only when the anticipated benefits to be derived from treatment exceed the possible risks to mother and fetus.

Usage in Children: The use of Sereniti (mesoridazine) in children under 12 years of age is not recommended, because safe conditions for its use have not been established. Attention should be paid to the fact that phenothiazines are capable of potentiating central nervous system depressants (e.g., anesthetics, opiates, alcohol, etc.) as well as atropine and phosphorus insecticides.

Precautions: While ocular changes have not to date been related to Sereniti[®] (mesoridazine), one should be aware that such changes have been seen with other drugs of this class.

Because of possible hypotensive effects, reserve parenteral administration for bedfast patients or for acute ambulatory cases, and keep patient lying down for at least one-half hour after injection.

Leukopenia and/or agranulocytosis have been attributed to phenothiazine therapy. A single case of transient granulocytopenia has been associated with Sereniti. Since convulsive seizures have been reported, patients receiving anticonvulsant medication should be maintained on that regimen while receiving Sereniti.

Neuroleptic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent in vitro, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of neuroleptic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time.

Information for Patients: Given the likelihood that some patients exposed chronically to neuroleptics will develop tardive dyskinesia, it is advised that all patients in whom chronic use is contemplated be given, if possible, full information about this risk.

Adverse Reactions: Drowsiness and hypotension were the most prevalent side effects encountered. Side effects tended to reach their maximum level of severity early with the exception of a few (rigidity and motoric effects) which occurred later in therapy.

With the exceptions of tremor and rigidity, adverse reactions were generally found among those patients who received relatively high doses early in treatment. Clinical data showed no tendency for the investigators to terminate treatment because of side effects. Sereniti[®] (mesoridazine) has demonstrated a remarkably low incidence of adverse

reactions when compared with other phenothiazine compounds.

Central Nervous System: Drowsiness, Parkinson's syndrome, dizziness, weakness, tremor, restlessness, ataxia, dystonia, rigidity, slurring, akathisia, motoric reactions (opisthotonos) have been reported.

Autonomic Nervous System: Dry mouth, nausea and vomiting, fainting, stuffy nose, photophobia, constipation and blurred vision have occurred in some instances.

Genitourinary System: Inhibition of ejaculation, impotence, enuresis, incontinence have been reported.

Skin: Itching, rash, hypertrophic papillae of the tongue and angioneurotic edema have been reported.

Cardiovascular System: Hypotension and tachycardia have been reported. EKG changes have occurred in some instances (see Phenothiazine Derivatives: Cardiovascular Effects).

Phenothiazine Derivatives: It should be noted that efficacy, indications and untoward effects have varied with the different phenothiazines. The physician should be aware that the following have occurred with one or more phenothiazines and should be considered whenever one of these drugs is used:

Autonomic Reactions: Miosis, obstipation, anorexia, paralytic ileus.

Cutaneous Reactions: Erythema, exfoliative dermatitis, contact dermatitis.

Blood Dyscrasias: Agranulocytosis, leukopenia, eosinophilia, thrombocytopenia, anemia, aplastic anemia, pancytopenia.

Allergic Reactions: Fever, laryngeal edema, angioneurotic edema, asthma.

Hepatotoxicity: Jaundice, biliary stasis.

Cardiovascular Effects: Changes in the terminal portion of the electrocardiogram, including prolongation of the Q-T interval, lowering and inversion of the T wave and appearance of a wave tentatively identified as a bifid T or a U wave have been observed in some patients receiving the phenothiazine tranquilizers, including Sereniti[®] (mesoridazine). To date, these appear to be due to altered repolarization and not related to myocardial damage. They appear to be reversible. While there is no evidence at present that these changes are in any way precursors of any significant disturbance of cardiac rhythm, it should be noted that sudden and unexpected deaths apparently due to cardiac arrest have occurred in patients previously showing characteristic electrocardiographic changes while taking the drug. The use of periodic electrocardiograms has been proposed but would appear to be of questionable value as a predictive device. Hypotension, rarely resulting in cardiac arrest, has been noted.

Extrapyramidal Symptoms: Akathisia, agitation, motor restlessness, dystonic reactions, trismus, torticollis, opisthotonos, oculogyric crises, tremor, muscular rigidity, akinesia.

Tardive Dyskinesia: Chronic use of neuroleptics may be associated with the development of tardive dyskinesia. The salient features of this syndrome are described in the **Warnings** section and below.

The syndrome is characterized by involuntary choreoathetoid movements which variously involve the tongue, face, mouth, lips, or jaw (e.g., protrusion of the tongue, puffing of cheeks, puckering of the mouth, chewing movements), trunk and extremities. The severity of the syndrome and the degree of impairment produced vary widely.

The syndrome may become clinically recognizable either during treatment, upon dosage reduction, or upon withdrawal of treatment. Movements may decrease in intensity and may disappear altogether if further treatment with neuroleptics is withheld. It is generally believed that reversibility is more likely after short rather than long-term neuroleptic exposure. Consequently, early detection of tardive dyskinesia is important. To increase the likelihood of detecting the syndrome at the earliest possible time, the dosage of neuroleptic drug should be reduced periodically (if clinically possible) and the patient observed for signs of the disorder. This maneuver is critical, for neuroleptic drugs may mask the signs of the syndrome.

Endocrine Disturbances: Menstrual irregularities, altered libido, gynecomastia, lactation, weight gain, edema. False positive pregnancy tests have been reported.

Urinary Disturbances: Retention, incontinence.

Others: Hyperpyrexia. Behavioral effects suggestive of a paradoxical reaction have been reported. These include excitement, bizarre dreams, aggravation of psychoses and toxic confusional states. More recently, a peculiar skin-eye syndrome has been recognized as a side effect following long-term treatment with phenothiazines. This reaction is marked by progressive pigmentation of areas of the skin or conjunctiva and/or accompanied by discoloration of the exposed sclera and cornea. Opacities of the anterior lens and cornea described as irregular or stellate in shape have also been reported. Systemic lupus erythematosus-like syndrome.

How Supplied:

Sereniti[®] Tablets, for oral administration: 10 mg, 25 mg, 50 mg, and 100 mg mesoridazine (as the besylate). Bottles of 100.

Sereniti[®] Ampuls, for intramuscular administration: 1 ml (25 mg mesoridazine (as the besylate)). Boxes of 20 and 100.

Sereniti[®] Concentrate, for oral administration: Contains 25 mg mesoridazine (as the besylate) per ml, alcohol, USP, 0.61% by volume.

Immediate containers: Amber glass bottles of 4 fl oz (118 ml) packaged in cartons of 12 bottles, with an accompanying dropper graduated to deliver 10 mg, 25 mg and 50 mg of mesoridazine (as the besylate).

Consult package insert before prescribing.

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*Intensive Psychodynamic Therapy With Borderline Patients:
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Control Groups for Psychosocial Intervention Outcome Studies
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1

Ativan® doesn't
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because of age or kidney or
liver dysfunction

2

Ativan® doesn't
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with numerous commonly
prescribed medications
(All benzodiazepines produce
additive sedative effects when
taken with alcohol or other
CNS depressants.)

3

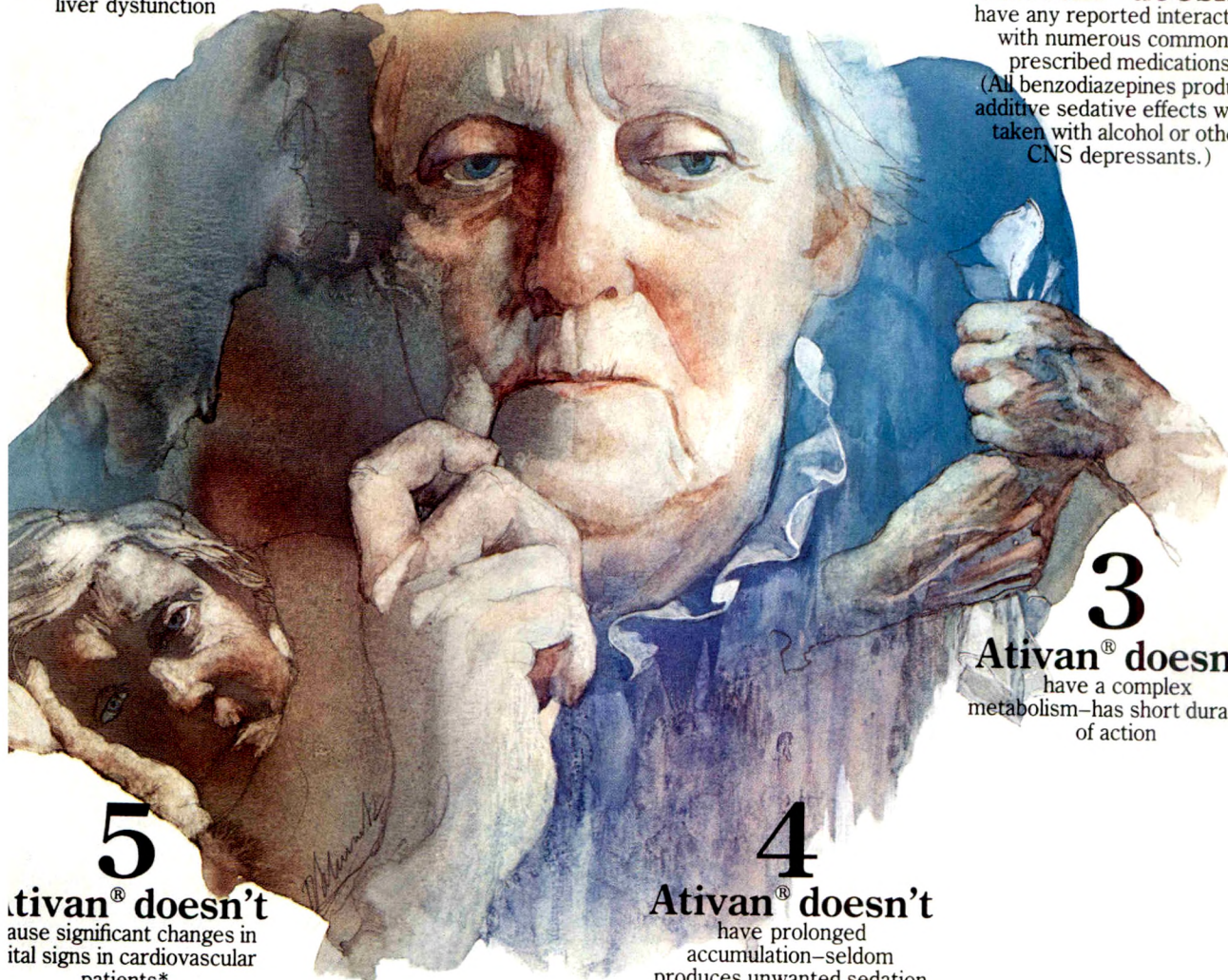
Ativan® doesn't
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metabolism—has short duration
of action

4

Ativan® doesn't
have prolonged
accumulation—seldom
produces unwanted sedation
(Sedation, reported in 15.9%
of patients in clinical trials, was
generally mild and transitory.)

5

Ativan® doesn't
cause significant changes in
vital signs in cardiovascular
patients*



...it does effectively relieve anxiety

Ativan®
(lorazepam)

*benzodiazepines have not been shown to be of benefit
in treating the cardiovascular component.

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rapid relief of anxiety

clearance not significantly delayed by age, liver or kidney dysfunction

cumulative sedative effects seldom a problem (Sedation, reported in 15.9% of patients in clinical trials, was generally mild and transitory.)

little likelihood of drug interaction (All benzodiazepines produce additive sedative effects when taken with alcohol or other CNS depressants.)

no significant changes in vital signs in cardiovascular patients*

short duration of action, simple metabolism

*Benzodiazepines have not been shown to be of benefit in treating the cardiovascular component.

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(lorazepam) [Ⓢ]

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Indicate one of the following on your prescriptions, as appropriate to your state laws:

- Do not substitute
- Dispense as written
- Medically necessary
- Brand necessary
- May not substitute
- No substitution
- NDPS (no drug product selection)

Brief Summary of Prescribing Information.

Indications and Usage: Management of anxiety disorders or short-term relief of symptoms of anxiety or anxiety associated with depressive symptoms. Anxiety or tension associated with stress of everyday life usually does not require treatment with an anxiolytic.

Effectiveness in long-term use, i.e., more than 4 months, has not been assessed by systematic clinical studies. Reassess periodically usefulness of the drug for the individual patient.

Contraindications: Known sensitivity to benzodiazepines or acute narrow-angle glaucoma.

Warnings: Not recommended in primary depressive disorders or psychoses. As with all CNS-acting drugs, warn patients not to operate machinery or motor vehicles, and of diminished tolerance for alcohol and other CNS depressants.

Physical and Psychological Dependence: Withdrawal symptoms like those noted with barbiturates and alcohol have occurred following abrupt discontinuance of benzodiazepines (including convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Addiction-prone individuals, e.g. drug addicts and alcoholics, should be under careful surveillance when on benzodiazepines because of their predisposition to habituation and dependence. Withdrawal symptoms have also been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic levels for several months.

Precautions: In depression accompanying anxiety, consider possibility for suicide.

For elderly or debilitated patients, initial daily dosage should not exceed 2mg to avoid oversedation. Terminate dosage gradually since abrupt withdrawal of any anxiolytic agent may result in symptoms like those being treated: anxiety, agitation, irritability, tension, insomnia and occasional convulsions. Observe usual precautions with impaired renal or hepatic function. Where gastrointestinal or cardiovascular disorders coexist with anxiety, note that lorazepam has not been shown of significant benefit in treating gastrointestinal or cardiovascular component. Esophageal dilation occurred in rats treated with lorazepam for more than 1 year at 6mg/kg/day. No effect dose was 1.25mg/kg/day (about 6 times maximum human therapeutic dose of 10mg/day). Effect was reversible only when treatment was withdrawn within 2 months of first observation. Clinical significance is unknown; but use of lorazepam for prolonged periods and in geriatrics requires caution and frequent monitoring for symptoms of upper G.I. disease. Safety and effectiveness in children under 12 years have not been established.

ESSENTIAL LABORATORY TESTS: Some patients have developed leukopenia; some have had elevations of LDH. As with other benzodiazepines, periodic blood counts and liver function tests are recommended during long-term therapy.

CLINICALLY SIGNIFICANT DRUG INTERACTIONS: Benzodiazepines produce CNS depressant effects when administered with such medications as barbiturates or alcohol.

CARCINOGENESIS AND MUTAGENESIS: No evidence of carcinogenic potential emerged in rats during an 18-month study. No studies regarding mutagenesis have been performed.

PREGNANCY: Reproductive studies were performed in mice, rats, and 2 strains of rabbits. Occasional anomalies (reduction of tarsals, tibia, metatarsals, malrotated limbs, gastroschisis, malformed skull and microphthalmia) were seen in drug-treated rabbits without relationship to dosage. Although all these anomalies were not present in the concurrent control group, they have been reported to occur randomly in historical controls. At 40mg/kg and higher, there was evidence of fetal resorption and increased fetal loss in rabbits which was not seen at lower doses. Clinical significance of these findings is not known. However, increased risk of congenital malformations associated with use of minor tranquilizers (chloridiazepoxide, diazepam and meprobamate) during first trimester of pregnancy has been suggested in several studies. Because use of these drugs is rarely a matter of urgency, use of lorazepam during this period should almost always be avoided. Possibility that a woman of child-bearing potential may be pregnant at institution of therapy should be considered. Advise patients if they become pregnant to communicate with their physician about desirability of discontinuing the drug. In humans, blood levels from umbilical cord blood indicate placental transfer of lorazepam and its glucuronide.

NURSING MOTHERS: It is not known if oral lorazepam is excreted in human milk like other benzodiazepines. As a general rule, nursing should not be undertaken while on a drug since many drugs are excreted in milk.

Adverse Reactions, if they occur, are usually observed at beginning of therapy and generally disappear on continued medication or on decreasing dose. In a sample of about 3,500 anxious patients, most frequent adverse reaction is sedation (15.9%), followed by dizziness (6.9%), weakness (4.2%) and unsteadiness (3.4%). Less frequent are disorientation, depression, nausea, change in appetite, headache, sleep disturbance, agitation, dermatological symptoms, eye function disturbance, various gastrointestinal symptoms and autonomic manifestations. Incidence of sedation and unsteadiness increased with age. Small decreases in blood pressure have been noted but are not clinically significant, probably being related to relief of anxiety.

Transient amnesia or memory impairment has been reported in association with the use of benzodiazepines.

Overdosage: In management of overdosage with any drug, bear in mind multiple agents may have been taken. Manifestations of overdosage include somnolence, confusion and coma. Induce vomiting and/or undertake gastric lavage followed by general supportive care, monitoring vital signs and close observation. Hypotension, though unlikely, usually may be controlled with Levarterenol Bitartrate Injection U.S.P. Usefulness of dialysis has not been determined.

DOSAGE: Individualize for maximum beneficial effects. Increase dose gradually when needed, giving higher evening dose before increasing daytime doses. Anxiety, usually 2-3mg/day given b.i.d. or t.i.d.; dosage may vary from 1 to 10mg/day in divided doses. For elderly or debilitated, initially 1-2mg/day; insomnia due to anxiety or transient situational stress, 2-4mg h.s.

HOW SUPPLIED: 0.5, 1.0 and 2.0mg tablets.

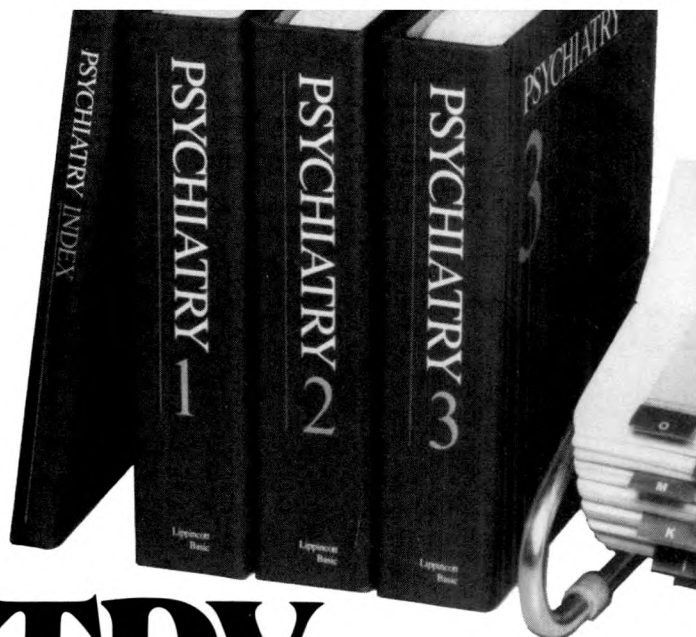


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TABLETS: 10 mg, 15 mg, 25 mg, 50 mg, 100 mg, 150 mg, and 200 mg thioridazine HCl, USP

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MELLARIL-S® (thioridazine) SUSPENSION: 25 mg/5 ml (each 5 ml contains thioridazine, USP, equivalent to 25 mg thioridazine HCl, USP) and 100 mg/5 ml (each 5 ml contains thioridazine, USP, equivalent to 100 mg thioridazine HCl, USP)

FOR ORAL ADMINISTRATION

Caution: Federal law prohibits dispensing without prescription.

Before prescribing or administering, see Sandoz literature for full product information. The following is a brief summary.

Contraindications: Severe central nervous system depression, comatose states from any cause, hypertensive or hypotensive heart disease of extreme degree.

Warnings: The risk of developing potentially irreversible *tardive dyskinesia* is believed to increase as duration of treatment and total cumulative dose increase, although it is impossible to predict who will develop the syndrome. It can also develop, although much less commonly, after brief treatment with low doses. Incidence appears to be highest among the elderly, especially elderly women. Generally chronic treatment should be reserved for chronically ill patients whose disease is most likely to respond to neuroleptic drugs and for whom other effective, less harmful treatment is not available or appropriate. There is no known treatment for *tardive dyskinesia* although the syndrome may partially or completely remit upon withdrawal of neuroleptic treatment. If signs and symptoms of *tardive dyskinesia* appear, drug discontinuation should be considered. Administer cautiously to patients who have previously exhibited a hypersensitivity reaction (e.g., blood dyscrasias, jaundice) to phenothiazines. Phenothiazines are capable of potentiating central nervous system depressants (e.g., anesthetics, opiates, alcohol, etc.) as well as atropine and phosphorus insecticides; carefully consider benefit versus risk in less severe disorders. During pregnancy, administer only when the potential benefits exceed the possible risks to mother and fetus.

Precautions: There have been infrequent reports of leukopenia and/or agranulocytosis and convulsive seizures. In epileptic patients, anticonvulsant medication should also be maintained. Pigmentary retinopathy, observed primarily in patients receiving larger than recommended doses, is characterized by diminution of visual acuity, brownish coloring of vision, and impairment of night vision; the possibility of its occurrence may be reduced by remaining within recommended dosage limits. Administer cautiously to patients participating in activities requiring complete mental alertness (e.g., driving), and increase dosage gradually. Orthostatic hypotension is more common in females than in males. Do not use epinephrine in treating drug-induced hypotension since phenothiazines may induce a reversed epinephrine effect on occasion.

Neuroleptic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent in vitro, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. Daily doses in excess of 300 mg should be used only in severe neuropsychiatric conditions.

Information for Patients: It is suggested that all patients who are candidates for chronic treatment be advised of the risk of *tardive dyskinesia*.

Adverse Reactions: *Central Nervous System*—Drowsiness, especially with large doses, early in treatment; infrequently, pseudoparkinsonism and other extrapyramidal symptoms; rarely, nocturnal confusion, hyperactivity, lethargy, psychotic reactions, restlessness, and headache. *Autonomic Nervous System*—Dryness of mouth, blurred vision, constipation, nausea, vomiting, diarrhea, nasal stuffiness,

and pallor. *Endocrine System*—Galactorrhea, breast engorgement, amenorrhea, inhibition of ejaculation, and peripheral edema. *Skin*—Dermatitis and skin eruptions of the urticarial type, photosensitivity. *Cardiovascular System*—ECG changes (see *Cardiovascular Effects* below). *Other*—Rare cases described as parotid swelling.

It should be noted that efficacy, indications and untoward effects have varied with the different phenothiazines. It has been reported that old age lowers the tolerance for phenothiazines; the most common neurological side effects are parkinsonism and akathisia, and the risk of agranulocytosis and leukopenia increases. The following reactions have occurred with phenothiazines and should be considered whenever one of these drugs is used:

Autonomic Reactions—Miosis, obstipation, anorexia, paralytic ileus. **Cutaneous Reactions**—Erythema, exfoliative dermatitis, contact dermatitis. **Blood Dyscrasias**—Agranulocytosis, leukopenia, eosinophilia, thrombocytopenia, anemia, aplastic anemia, pancytopenia. **Allergic Reactions**—Fever, laryngeal edema, angioneurotic edema, asthma. **Hepatotoxicity**—Jaundice, biliary stasis. **Cardiovascular Effects**—Changes in the terminal portion of electrocardiogram including prolongation of Q-T interval, lowering and inversion of T-wave, and appearance of a wave tentatively identified as a bifid T or a U wave have been observed with phenothiazines, including Mellaril (thioridazine); these appear to be reversible and due to altered repolarization, not myocardial damage. While there is no evidence of a causal relationship between these changes and significant disturbance of cardiac rhythm, several sudden and unexpected deaths apparently due to cardiac arrest have occurred in patients showing characteristic electrocardiographic changes while taking the drug. While proposed, periodic electrocardiograms are not regarded as predictive. Hypotension, rarely resulting in cardiac arrest. **Extrapyramidal Symptoms**—Akathisia, agitation, motor restlessness, dystonic reactions, trismus, torticollis, opisthotonus, oculogyric crises, tremor, muscular rigidity, and akinesia. **Tardive Dyskinesia**—Characterized by involuntary choreoathetoid movements variously involving the tongue, face, mouth, lips or jaw (e.g., protrusion of the tongue, puffing of the cheeks, puckering of the mouth, chewing movements), trunk and extremities—may be recognized during treatment upon dosage reduction or withdrawal of treatment. Movements may decrease or disappear if further treatment is withheld, although this reversibility is more likely after short-term rather than long-term treatment. Since neuroleptics may mask the signs of *tardive dyskinesia*, reducing dosage periodically increases the likelihood of detecting the syndrome at the earliest possible time. **Endocrine Disturbances**—Menstrual irregularities, altered libido, gynecomastia, lactation, weight gain, edema, false positive pregnancy tests. **Urinary Disturbances**—Retention, incontinence. **Others**—Hyperpyrexia; behavioral effects suggestive of a paradoxical reaction, including excitement, bizarre dreams, aggravation of psychoses, and toxic confusional states; following long-term treatment, a peculiar skin-eye syndrome marked by progressive pigmentation of skin or conjunctiva and/or accompanied by discoloration of exposed sclera and cornea; stellate or irregular opacities of anterior lens and cornea; systemic lupus erythematosus-like syndrome.

Dosage: Dosage must be individualized according to the degree of mental and emotional disturbance, and the smallest effective dosage should be determined for each patient.

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Self-Portrayal by a Depressed Poet: A Contribution to the Clinical Biography of William Cowper

Joachim-Ernst Meyer, M.D., and Ruth Meyer

The life of the eighteenth-century English poet William Cowper, who suffered from recurrent major depression, or bipolar II disorder, is described. Since no effective treatment was available, Cowper's writings give an example of the natural history of major depression. They also illustrate the fate of a mental patient of the upper classes at that time. The authors discuss the relevance of Cowper's mother's death during his childhood to his depressive illness and draw attention to the poet's sensitive description of his own psychopathology and the lifelong course of his illness.

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William Cowper, the eighteenth-century English poet, who lived from 1731 to 1800, suffered from melancholia. His "Memoir" and particularly his letters, which are hardly known, vividly describe his illness and provide a valuable insight into the situation of the mentally ill at that time.

The "Memoir" is based on a narrative written after Cowper's hospitalization at St. Albans and was intended only for his closest friends. In spite of his refusal to allow publication of this manuscript, two separate editions appeared in 1816. In 1953 the most recent edition was published in the *Proceedings of the American Philosophical Society*, edited by the English scholar M.J. Quinlain (1) (see also reference 2).

Received May 15, 1985; revised Feb. 5, 1986; accepted March 13, 1986. From the Department of Psychiatry, University of Göttingen. Address reprint requests to Dr. Meyer, Department of Psychiatry, University of Göttingen, v.-Siebold-Str. 5, D-3400 Göttingen, Federal Republic of Germany.

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The memoirs begin with Cowper's childhood and adolescence, followed by a detailed description of his most severe emotional breakdown in 1763. The course of his illness—including his admission to the Collegium Insanorum in St. Albans, his recovery, and his discharge—is carefully documented in a literary style that in places resembles a diary.

Our information about Cowper's subsequent life and the later recurrences of depression is based on the three-volume work *The Life and the Posthumous Writings of William Cowper*, written by his younger friend William Hayley and published in 1803-1804 (3). Along with several poems and a short biography, this work includes 419 letters—most of them dated—from Cowper to friends and relatives. (Except where otherwise stated, all references in this paper to Cowper's life after his discharge from the Collegium Insanorum are taken from this work.)

BIOGRAPHICAL DATA

William Cowper was born in Berkhamsted, Hertfordshire. He was the son of the local vicar, whose own father was a well-known lawyer; his mother, Ann, was a descendant of the seventeenth-century poet John Donne. His mother's untimely death when he was only 6 years old was one of the most traumatic events in Cowper's life. Thereafter, as a schoolboy, he suffered from the cruelty of an older pupil. Furthermore, because of "very weak eyes," when he was 8 years old he had to spend a year in the home of an ophthalmologist.

At the age of 10, Cowper was sent to Westminster, the famous London public school. On leaving school he decided to study law; he took up residence for a period of 3 years in the Temple, the London law college, and for practical experience he was affiliated with a London barrister. During this time he suffered

from his first depressive attack, which lasted several months.

The 10 years that followed were happy and creative ones, spent among his friends and relatives, writing poetry and letters. It was during this period that he became engaged to his cousin Theodora, to whom many of his poems are addressed, but her father refused permission for their marriage.

At the age of 33, Cowper applied for the post of Clerk to the Journals of the House of Lords. At this time he began to mention a "nervous fever," which quickly grew worse. A summer holiday brought a slight improvement, but his "misery" overtook him again on his return to work. After he had made several suicide attempts, his brother arranged his admission to the Collegium Insanorum in St. Albans.

On his discharge from the hospital 18 months later, Cowper chose to live alone in Huntingdon, near Cambridge, not wishing any contact with his former London friends. Here he made the acquaintance of the Reverend Unwin and his family and soon became a boarder in their house, feeling secure and comforted by the atmosphere of piety surrounding him.

Cowper belonged to the Calvinist branch of the Revivalist Movement, which, under the direction of John Wesley, was contained initially within the Anglican Church; it separated later to become the Free Methodist Church (4). Cowper's physician at St. Albans, Dr. Cotton, was an evangelist, too (5).

When the Reverend Unwin died, a year after Cowper came to live with the family, Cowper decided to remain with Mrs. Unwin. The couple moved to Olney, a poverty-stricken town on the river Ouse. Cowper described his relationship to Mrs. Unwin as one of deep Christian friendship. In Olney, Cowper met John Newton, the one-time slave dealer turned zealous evangelist. Newton's influence on him was profound and led him to write a series of hymns that are still known as the Olney hymns.

As a poet Cowper belongs with the preromantics. His first book of poems appeared in 1782. Stimulated by his friendship with Lady Austin, a widowed evangelist lady, he wrote the ballad "John Gilpin," his most popular work. It was also during this fruitful period that he began his free translation of Homer. Increasing acclaim for his literary talents brought a wider circle of friends, but his feeling of well-being was always marred by a sense of foreboding "that a cloud may come over me—but from clouds I was never exempted" (3, vol. I, p. 199).

Early in 1790 Cowper became slightly depressed again. Although he was sometimes too disabled to write letters or participate in social activities, he did from time to time continue to work on his translation of Homer, the last revised edition of which appeared in 1791 in Cambridge. By 1793 Mrs. Unwin had become incapacitated from a stroke, and Cowper remained so depressed that his cousin, Lady Hesketh, felt obliged to come and live with them, organizing their care and financial support. In 1796 Mrs. Unwin died. Even this

event did not appear to move him emotionally. During the last few years of his life, he was occasionally able to write creatively. His final poem, "The Castaway," was written in March 1799. In this work he succeeded in vividly expressing the despair and helplessness of his melancholic state. He died on April 25, 1800, at the age of 69.

COURSE OF THE ILLNESS

Description in Cowper's Memoirs

Cowper's first depressive phase occurred in 1752, at the beginning of his legal studies, when he took up residence in the Temple. Here he was overcome by a "dejection of the spirits," which he said no one could comprehend who had not experienced such a feeling. "Day and night I was upon the rack, lying down in horror and rising in despair." He lost all interest in his studies and spent his time reading poems. "Though I found not here what I might have found, a cure for my malady, yet it never seemed so much alleviated as while I was reading." During this first depressive phase, for which his biography supplies no recognizable precipitating cause, Cowper experienced what he called the "inefficacy of all human means."

Quite suddenly, while Cowper was on holiday, his depression disappeared. He described it in his memoirs: "The morning was clear and calm; the sun shone bright upon the sea. Here it was that on a sudden, as if another sun had been kindled that instant in the heavens on purpose to dispel sorrow and vexation of spirit, I felt the weight of all my misery taken off; my heart became light and joyful in a moment." He was first moved by a sense of gratitude to God, who he believed had heeded his prayers and granted him a recovery. But, as he added, the devil and his own wickedness would soon have him believe that his sudden recovery was more likely due to the change of surroundings and the "amusing varieties of the place."

Ten years went by before Cowper fell ill again in 1763, this time in a particularly difficult situation. He had been offered the post of Clerk to the Journals of the House of Lords because the incumbent, a relative of Cowper and already advanced in years, wished him to become his successor. When Cowper began to prepare himself for his new responsibilities, the signs of a breakdown became apparent. He began to brood over his imagined guilt in wishing death on his relative. As the day drew nearer when he was to take up his new duties, his anxiety and agitation grew worse. He tried taking medication prescribed for him by a physician, but without effect. Sometimes he expressed the hope of becoming insane before he could take up his new post; at other times he comforted himself with the thought of suicide—"I considered life as my property"—and procured laudanum for himself. He even contemplated fleeing to France and taking holy orders, but the urge to commit suicide gradually gained the upper hand.

His repeated attempts at suicide included throwing himself into the Thames, poisoning himself with laudanum, stabbing himself in the heart, and, as a last resort, hanging himself. During this time he was continually brooding about which alternative was the most painful to endure, the "enormity of the crime" of suicide or the torment of living. Eventually, when even the attempt at hanging failed, he abandoned himself to utter despair: "A sense of self-loathing and abhorrence runs through all my insanity." He would sleep for perhaps 3 hours, only to awaken with "ten times a stronger alienation from God than ever." He now began to take laudanum not to kill himself but "to stupefy my awakened and feeling mind, harassed with sleepless nights and days of uninterrupted misery." He no longer went out-of-doors, believing that passers-by would jeer and despise him and fearing that the voice of his conscience could be heard by others. "The accuser of the brethren was ever busy with me night and day, bringing to my recollection . . . long forgotten sins and charging upon my conscience things of indifferent nature as atrocious crimes."

In December 1763 Cowper was admitted to the Collegium Insanorum at St. Albans under the care of Dr. Nathaniel Cotton. In his memoirs he drew "a veil over the secrets of my prison-house," but he gave a clear description of his remission, which set in 8 months later. It began with "a vague presage of better things at hand without being able to assign a reason for it." After a night of pleasant dreams, he awoke refreshed, "with a sensation of delight in my mind. . . . My joy was as much a mystery to myself as to those about me." Cowper experienced his recovery as deliverance by God and was so stirred by it emotionally that for weeks he was unable to speak of Christ or the Gospels without tears filling his eyes. "To rejoice day and night was all my employment. Too happy to sleep much, I thought it was but lost time that was spent in slumber." Because of this "sudden transition from despair to joy," Dr. Cotton feared that Cowper's condition could "terminate in a fatal frenzy"—in other words, in a manic psychosis. For this reason the doctor counseled Cowper to remain for another year in St. Albans.

Description of the Illness in Cowper's Letters

At this point the "Memoir" comes to a close, but the letters Cowper wrote after his discharge from St. Albans reveal his changed attitude to life: "The only recompense I can make you for your kind attention to my affairs, during my illness, is to tell you, that by the mercy of God I am restored to perfect health both of mind and body" (3, vol. I, p. 34). He prayed that this feeling would always remain with him: "Then I am sure, I shall continue to be as I am at present, really happy" (3, vol. III, p. 376). He wrote of Mrs. Unwin, after he had joined her family, "The lady regards me with a friendship so truly Christian, that I almost fancy my own mother restored to life again," and saw in her

the compensation for all the friends he lost through his illness (3, vol. I, p. 40). During this time he also saw his brother frequently and felt better in his company than he had for many years: "I am much happier than the day is long, and sun-shine and candle-light alike see me perfectly contented" (3, vol. I, p. 37).

At the beginning of 1770, Cowper's brother became ill and died within a few months. In the autumn of the same year, Cowper was depressed for a short time, but his second severe melancholic phase did not begin until 1773, when he again became suicidal. Newton tried to cure him through prayer and exorcism. Several months went by before Newton finally felt compelled to call in Dr. Cotton again. "He replied that he could do no more for me than might be done at Olney, but recommended particular vigilance lest I should attempt my life—a caution for which there was the greatest occasion" (6).

Cowper remained depressed for almost 7 years without intermission and did not begin writing again until the autumn of 1780, when his melancholia finally remitted. On his recovery he wrote a letter to Lady Hesketh:

Know then, that in the year 1773, the same scene that was acted at St. Albans, opened upon me again at Olney, only covered with a still deeper shade of melancholy, and ordained to be of much longer duration. I was suddenly reduced from my wonted rate of understanding to an almost childish imbecility. I did not, indeed, lose my senses, but I lost the power to exercise them. I could return a rational answer, even to a difficult question; but a question was necessary, or I never spoke at all. This state of mind was accompanied, as I suppose it to be in most instances of the kind, with misapprehensions of things and persons, that made me a very untractable patient. I believed that everybody hated me, and that Mrs. Unwin hated me most of all. (6)

From 1780 onward Cowper was again restored to full health and busy with his writing. During this especially productive phase he wrote in a letter to his cousin: "Set me down, therefore, my dear, for an industrious rhymers, so long as I shall have the ability for either to honour God or to serve man, or even to serve myself" (7).

In 1787 Cowper suffered another brief attack of depression associated with a suicide attempt. The nature and course of this depressive phase are particularly well documented in his correspondence. On January 8, 1787, he wrote: "I have had a little nervous fever lately, my dear, that has somewhat abridged my sleep, and though I find myself better today than I have been since it seized me, yet I feel my head lightish, and not in the best order for writing" (3, vol. I, p. 236). He wrote in a second letter on the same day:

My nights during this whole week may be said to have been almost sleepless. The consequence has been, that except the translation of about thirty lines at the conclusion of the 13th Book, I have been forced to abandon Homer entirely. But Homer's battles cannot be fought by

a man who does not sleep well, and who has not some little degree of animation in the day time. Last night, however, quite contrary to my expectations, the fever left me entirely, and I slept quietly, soundly, and long. If it please God that it return not I shall soon find myself in condition to proceed. (3, vol. I, p. 238)

The third letter, dated July 1787, said: "This is the first time I have written these six months, and nothing but the constraint of obligation could induce me to write now. . . . In my present state of mind I taste nothing; nevertheless I read; partly from habit, and partly because it is the only thing that I am capable of" (3, vol. I, p. 240).

In 1792 Mrs. Unwin suffered a stroke, which resulted in her almost total dependence on Cowper's care. Writing to Lady Hesketh of this misfortune, Cowper added: "I am as well myself as you have ever known me, and study in a room exposed to all manner of inroads. It is on the ground floor, the room in which we dine, and in which I am sure to be found by all who seek me. They find me generally at my desk, and with my work, whatever it be, before me" (3, vol. II, p. 11).

Early in 1793, Cowper's melancholia deepened. This depression was very severe at times and was to persist, with fluctuations, until his death. At its onset, Cowper scarcely agreed to take any nourishment. For a period of several weeks he appears to have been completely mute, as we see from his reaction to the death of Mrs. Unwin in December 1796. Hayley (3) remarked on this, saying that "instead of mourning the loss of a person, in whose life he had seemed to live, all perception of that loss was mercifully taken from him. . . . He appeared to have no memory of her having existed, for he never asked a question concerning her funeral, nor ever mentioned her name" (3, vol. II, p. 205).

In the autumn of 1797, Cowper's state of mind improved sufficiently to allow him to work until the spring of 1799 on the revision of his Homer translation. He died a year later, presumably of a heart insufficiency that had been causing edema of the legs during the last weeks. In his last known letter to Lady Hesketh, dated October 1798, he wrote: "You describe delightful scenes, but you describe them to one who, if he even saw them, could receive no delight from them. . . . In one day, in one minute, I should rather have said, she [nature] became an universal blank to me, and though from a different cause, yet with an effect as difficult to remove, as blindness itself" (3, vol. II, p. 212).

COWPER: A MENTAL PATIENT IN THE EIGHTEENTH CENTURY

The Collegium Insanorum, where Cowper was admitted at the request of his brother, was founded in 1745 by Dr. Cotton, a graduate of Leyden University.

Dr. Cotton had worked for some time in a similar institution for the mentally ill before founding the Collegium Insanorum. In Cowper's "Memoir" and also in his letters, there is no mention of the therapeutic atmosphere in the Collegium or of special treatment for psychotic patients. We know only about Dr. Cotton's relationship to Cowper during the extra year he remained there: "He visited me every morning, while I stayed with him after . . . my recovery and the gospel was the delightful theme of our conversation." This suggests that Dr. Cotton, who belonged to the same religious community as Cowper did, could help the patient by lessening his fear of damnation and pointing to God's redemption.

"Private madhouses" came into being in England after a law was passed in 1714 that allowed a distinction to be made between the legal status of the mentally ill and that of "Rogues, Vagabonds, Sturdy Beggars and Vagrants." The consequence was that, with the consent of at least two justices of the peace, such patients could be placed under parish jurisdiction and committed to a madhouse. In 1774, statutory regulations were published governing the issuing of a license to open a private madhouse, including rules for its inspection.

By the end of the eighteenth century, quite a number of doctors had become owners of such institutions, which then remained family property for several generations. The tradition of private madhouses in England finally came to an end with the disclosure of their abuses, and in 1845 legal provision was made for the establishment of the much larger regional and municipal asylums for the poorer mentally ill (8).

The most difficult problem facing the private institutions was their lack of experienced nursing staff. It therefore seems scarcely surprising that Dr. Cotton only reluctantly gave his permission for Cowper to take his attendant, Samuel Roberts, with him on his discharge from the hospital. Roberts remained with Cowper for 30 years. Such privileges could be realized only by those belonging to the upper social classes. This must also have been the presupposition for admission to St. Albans, where the weekly costs averaged 3-5 guineas (9).

During his final depressive phase, Cowper mentioned treatment with asses' milk and with laudanum, a weak opium preparation. (Tincture of opium was in fact regularly used well into the twentieth century as a treatment for depression—in particular, agitated depression—before the introduction of antidepressive drugs.) Cowper reported that 12 drops of laudanum were sufficient to ensure a good night's sleep. One of the doctors consulted by Cowper around this time was Dr. F. Willis, who had achieved widespread recognition for his treatment of King George III, who suffered from recurrent psychoses (10). Dr. Willis prescribed drugs for Cowper, but when they did not help, he called to see him personally in Weston. There he expressed the opinion that "a change of air, scene and circumstances" would do Cowper good.

DIAGNOSTIC AND CLINICAL COMMENTS

William Cowper, who died at age 69 years, suffered from recurrent major depressions, only one of which led to psychiatric hospitalization and was followed (in the way of a "switch process") by a temporary hypomanic state. Altogether there were three shorter, or slighter, depressive phases and three longer ones that were more severe. Because of the one temporary hypomanic fluctuation, which induced his physician to retain him as an inpatient for another year, Cowper's case would be classified according to *DSM-III* as an atypical bipolar disorder (296.70), or bipolar II. A clear mania never occurred. As Cowper commented: "I have not that which commonly is a symptom of such a case. I mean extraordinary elevation. When I am in the best health, my tide of animal sprightliness flows with great equality, so that I am never, at any time exalted in proportion as I am sometimes depressed" (3, vol. I, p. 195).

The free intervals, which commonly become shorter during the course of the illness (11), did not vary for Cowper, but the length of the depressive phases increased. Both the phase that started when he was 52 years old and the last one, which persisted until his death, were continuous for 7 years. The psychotic character of the depressions was most marked during the second attack, when he became an inpatient. He had to be hospitalized because of the high risk of suicide, his religious delusions of guilt (his conviction that he was eternally damned, his despair of receiving mercy [7]), and his mood-congruent auditory hallucinations (the voice of his conscience seeming to become audible to others and his perception of the demanding voice of God). In the later depressions, feelings of guilt occurred, too, but they did not dominate as they did during the second attack.

In each depressive phase there were, as the letters Cowper wrote during reconvalence illustrate, loss of activity, avoidance of social contact, and lack of animation. The latter escalated to a state of "lost emotions" and derealization, during which he totally lost contact with reality and was paralyzed in his literary productivity: "I live in a world abounding with incidents upon which many grave, and perhaps some profitable observations might be made; but those incidents never reaching my unfortunate ears, both the entertaining narrative and the reflections it might suggest, are to me annihilated and lost" (3, vol. III, p. 182). In a similar way his relations to his fellow men changed: "It seems almost incredible to myself, that my company should be at all desirable to you, or to any man. I know so little of the world as it goes at present" (3, vol. I, p. 292).

In Cowper's depressive phases, insomnia with early morning waking was of great importance. Often it was the initial symptom of a new depressive attack, and, correspondingly, a night in which he slept well could be the forecast of his usually rapid recovery. In addition there were typical diurnal mood swings:

"rising cheerless and distressed in the morning, and brightening a little as the day goes on" (3, vol. II, p. 93).

With regard to events meaningfully related to the onset of his depressive phases, Cowper's case is inconsistent. The second and worst phase occurred during an extreme professional conflict; the shorter attack 6 years later can also be related to the preceding death of his brother. For the other four phases, a relationship to reactive factors cannot be found. Neither the forbidden marriage to Theodora nor the sudden death of his friend, the son of Mrs. Unwin, was followed by depression. His already marked depressive state did not worsen after the death of Mrs. Unwin.

Nothing is known about mental disorders in Cowper's family. On the other hand, the death of his mother when he was 6 years old is possibly relevant to his later illness. His mother's death was followed by his first difficult school years and the 1-year stay with the family of the ophthalmologist. The two later events were described by Cowper in his memoirs, but the death of his mother remains unmentioned. In life-event studies, maternal death in childhood is considered to be the best documented factor contributing to a disposition toward affective disorders in later life. However, there are still many objections against positing such a direct relationship, i.e., methodological deficits and uncritical interpretations of the results of such studies (12, 13).

In the eighteenth century there was no effective treatment for depression. Thus, Cowper's biography, documented in his memoirs and then in his letters covering the years until his death, is a clear example of the natural history of major depression. This can rarely be observed today because of modern antidepressive treatment and prophylaxis. In addition, the predominant themes of depressive brooding and particularly the delusional thought content have changed over time. What von Orelli (14) has described as happening between 1878 and 1951—the lessening and rarity of religious guilt feelings—holds true even more when the present is compared with Wesleyan England. Thus, it is surprising that from the standpoint of modern clinical psychiatry, Cowper's clinical picture, after 200 years, gives no reason for diagnostic uncertainty. The episodic type of the depression, the spontaneous remissions, the main symptoms, and the restitution to full literary creativity confirm the diagnosis.

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Levels of Emotional Awareness: A Cognitive-Developmental Theory and Its Application to Psychopathology

Richard D. Lane, M.D., and Gary E. Schwartz, Ph.D.

The authors present a cognitive-developmental theory of emotional awareness that creates a bridge between normal and abnormal emotional states. Their primary thesis is that emotional awareness is a type of cognitive processing which undergoes five levels of structural transformation along a cognitive-developmental sequence derived from an integration of the theories of Piaget and Werner. The five levels of structural transformation are awareness of 1) bodily sensations, 2) the body in action, 3) individual feelings, 4) blends of feelings, and 5) blends of blends of feelings. The authors suggest applications of this model to current unresolved problems in psychiatric theory, research, and practice.

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The importance of emotion to the field of psychiatry cannot be overemphasized. A disturbance of emotion may well occur in every diagnostic category: in addition to the affective disorders and anxiety disorders, disturbances in emotion are fundamental aspects of schizophrenia, organic mental disorders, psychosomatic disorders, and personality disorders. In fact, it could be argued that emotional disturbance is so fundamental to the concept of mental disorder that the absence of emotional disturbance as a major feature of a diagnostic category is evidence for the inadequacy of the conceptualization of the category itself, not the unimportance of emotion.

When we speak of a disturbance of emotion, however, we seem to imply that a coherent framework exists which one can use to understand the nature of normal as well as psychopathological emotional states. The fact of the matter is that emotion is a complex phenomenon which is only incompletely understood.

Received July 29, 1985; revised Feb. 24, 1986; accepted April 4, 1986. From the Departments of Psychiatry and Psychology, Yale University, New Haven, Conn. Address reprint requests to Dr. Lane, Department of Psychiatry and Behavioral Sciences, Chicago Medical School, 3333 Green Bay Rd., North Chicago, IL 60064.

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Most theorists agree that emotion consists of a physiological or biological component, an experiential or psychological component, and an expressive or social component (1-3). At present, the relationship between these different components is not well understood (4). Although major deficits exist in our understanding of each of the three domains of emotion independent of the others, the experiential domain is the one we deal with most in clinical situations and may therefore be the one domain where improvements in our understanding are most needed.

The importance of the experiential domain in clinical work is immediately evident from the fact that most patients seek help because they experience distress: they don't feel well in an emotional sense, especially in their relationships with others. Medication is often prescribed to relieve excessive experiences of anxiety, depression, euphoria, or rage. Judgments about whether medication is necessary are based on issues such as how pervasive or disruptive the emotional experience in question is in relation to the rest of the patient's emotional life, as well as the patient's capacity to deal with the unpleasant feelings by psychological or behavioral means. Similar considerations apply to the use of behavioral techniques such as relaxation training and systematic desensitization. Our tools for making explicit, rational judgments of this sort are limited and are usually considered part of the "art" of good clinical care. A new theory of emotional experience could provide a framework for making such judgments on a more objective basis.

An alternative or adjunct to medication or behavioral therapy is psychotherapy. Much of psychotherapy consists of helping patients to clarify what they are feeling, understand the origins of their feelings, and tolerate their intense emotional states better while minimizing the tendency to exclude these states from conscious awareness. However, the conceptual framework we have at present for understanding individual differences in the emotional lives of patients and the changes that occur in the experience of emotion during the course of treatment is quite limited. Without a conceptual framework of this sort, we lack a rational basis for deciding how to tailor psychotherapeutic technique to the needs of a particular patient or how to make adjustments in technique during the course of psychotherapy.

Nevertheless, it would be inaccurate to imply that we are devoid of any conceptual tools to guide us in the conduct of our clinical work in these areas. Since Freud, ego psychologists and object relations theorists (5-8) have demonstrated the usefulness of a cognitive-developmental approach in understanding the nature of the differences in the mental experiences of patients with different degrees of psychopathology and how the process of psychotherapy leads to clinical change. A central organizing concept in these formulations is that of psychic structure. From a clinical rather than a metapsychological standpoint, psychic structure refers to the degree of differentiation and integration of the contents of mental activity (9). The concept has achieved its greatest clarity and clinical applicability as it is applied to self and object representations (9). Although object relations theorists have for a long time recognized an association between object representation and emotion or affect, the discussion of emotion from a cognitive-developmental perspective has not yet been clearly differentiated from object relations theory.

For example, Novey (5) hypothesized that internal representations of objects are affective experiences which are only secondarily perceived to have ideational content. Schmale (6) proposed that affective experiences and object representations originate from a common matrix and discussed how emotional experience becomes more differentiated with development by virtue of interaction with significant others. Mahler et al. (7) discussed how the development of a basic mood depends on the child's affective experience during the practicing and rapprochement subphases of the separation-individuation process and how the establishment of an easily recallable mental representation of the mother (i.e., object constancy) is a prerequisite for the capacity to maintain an awareness of a variety of feelings for the mother despite the immediate circumstances. Blatt (8) proposed that two types of depression, an anaclitic and an introjective type, may be distinguished on the basis of the degree of differentiation and integration of the object representations which accompany the two different types of depressive experience. These contributions suggest that a specifiable relationship may exist between emotional experience and object representation on the basis of a cognitive-developmental perspective. However, a comprehensive framework for thinking about changes in the experience of emotion from a cognitive-developmental perspective distinct from object representations has been lacking.

The purpose of the present paper is to fill this gap in the clinical literature. Our primary thesis is that emotional awareness is a type of cognitive processing which undergoes five levels of structural transformation along a cognitive-developmental sequence derived from an integration of the theories of Piaget and Werner. The theoretical basis for this new formulation will be discussed first, followed by a description of five levels of emotional awareness. We conclude with a

discussion of the implications of this new model for psychiatric theory, research, and practice.

INFLUENCE OF COGNITION IN STRUCTURING INTERNAL REALITY

Ever since Einstein and Heisenberg, our conception of reality has undergone a radical transformation (10). Their work and that of other modern physicists has led to the conclusion that there is no such thing as a tangible (i.e., completely measurable) objective reality. Rather, our conception of external reality is observer-dependent in the sense that no absolute standard exists against which the accuracy of one's perception of reality can be judged correct or incorrect. This view is supported by a long tradition of work in experimental psychology demonstrating that past experience and mental set contribute significantly to what is perceived in the external world (11). The best that one can hope to do is account for as much information as one can in one's description of the external world until another perspective comes along which can account for more information. The prevailing view at the time is what we refer to as consensual reality.

For the present state of our knowledge about emotion, there is no consensus. Perhaps one important reason for this lack of consensus is the assumption by some that emotion is a phenomenon which has a tangible reality. This perspective is best exemplified by researchers who view the objective measurement of physiological arousal (biological domain) and/or the objective measurement of behavioral expression (social domain) to be adequate measures of emotion. Such a perspective avoids the vagaries associated with the objective assessment of emotional experience because there is no possible way to get inside a person and determine with certainty what it is that a person experiences. But if emotional experience does not have a tangible, objectively verifiable reality, what sort of reality does it have?

The answer, of course, is an observer-dependent reality. Although, in agreement with Lazarus (12), we adopt the position that emotion is preceded by a cognitive appraisal of the environment, which in turn leads to the activation of emotion, we do not mean that emotional experience is observer-dependent in this sense. Rather, our focus is on the structure of experience once an emotional response has been activated. Our central thesis is that what is experienced as emotion is the consequence of a subsequent cognitive processing of emotional arousal and that the cognitive process itself undergoes a sequence of structural transformations during development which, in turn, determines the structure of subsequent emotional experience. Thus, emotional experience is observer-dependent in the sense that it is the structural organization of cognitive processing which determines the structure of the individual's experience. Although we use the terms "emotional experience" and "emotional

awareness" interchangeably, we use the latter term to highlight the important role that conscious cognition plays in experience.

This perspective on emotional experience can be illustrated with an analogy regarding the influence of cognitive processes on the perception of external reality. The Eskimos are known to have at least 30 different words for snow of different varieties (13). Eskimo children learn the concepts captured by the words and become able to perceive the 30 or so different varieties of snow. In contrast, children growing up in Florida never learn these words, do not develop the concepts, and do not perceive these distinctions in the environment. Although faced with "the same" external reality, the children from Florida would perceive a snowy landscape as undifferentiated, compared with the more differentiated view of the Eskimo children. One could say that the "snow awareness" of the Eskimo children was structurally transformed during development, which in turn determined the structure of their experience of the external world. Although one might claim (correctly) that the Eskimos are better able to perceive what is "really there," this does not by any means imply that these 30 or so words capture all of the useful distinctions which could potentially be made between different types of snow.

In a similar way, emotional arousal constitutes an internal world about which one has knowledge, and it is the structural organization of this knowledge that determines how the internal world of emotion is experienced. In a manner analogous to the example of snow, the internal world of emotional arousal has the potential to be perceived or introspected in an infinite number of ways, limited only by the knowledge one has beforehand of one's own emotional life. Each addition to this structure is added to what has already been acquired. These additions to knowledge can thus be thought of as hierarchical, which in turn can be viewed as generating a hierarchical layering of levels of awareness of one's internal world.

This example suggests that individuals differ from one another in the structural organization with which they possess emotional arousal. It also suggests that this structural organization is reflected in the verbal representations used to describe the content of what is perceived. However, this perspective is not reflected at present in the design of instruments currently in use to assess emotional experience. For example, instruments such as the Taylor Manifest Anxiety Scale (14), the Hamilton Rating Scale for Depression (15), the Profile of Mood States (16), the State-Trait Anxiety Inventory (17), and the Differential Emotion Scale (18) specify the emotion or mood and ask the respondent to quantify the intensity or frequency of that experience on a categorical or ordinal scale. The structure of the experience in question—its degree of differentiation and integration—is thus determined by the instrument. This raises the question of whether individuals who achieve identical scores on such self-report instruments might report very different experiences if they were

allowed to determine the structure of the verbal representations themselves.

A report by Sommers (19) suggested that individual differences do exist in the structure of representations used to depict emotion and that such structural characteristics can be objectively assessed. The main finding in Sommers's report was that the range of emotions experienced, as determined by the numerical variety of emotional responses spontaneously reported by a person in response to standard stimuli, correlated positively with the cognitive complexity with which other people were described and the presence of the relatively advanced cognitive capacity to assume the role of different participants in an interpersonal interaction. In contrast to the traditionally dominant view of cognition as standing in opposition to emotion, this study suggested that an advanced cognitive organization can be associated with a greater rather than a lesser degree of emotional organization. It also provides empirical support for the notion that the cognitive complexity of object representation corresponds to the cognitive complexity of emotional experience.

TRANSFORMATIONS DERIVED FROM DEVELOPMENTAL THEORY

The view that symbolic processes determine the nature of experience has been elaborated in great detail by Werner and Kaplan (20). These authors argued that acts of depiction serve the function of constructing a world which becomes known in the process of such an act, not simply reproducing previously formed conceptions, as Piaget believed (21). Through acts of depiction, a person can make explicit, can formulate, features of experience that would otherwise remain fluid, embedded, and inaccessible to self and others. Werner and Kaplan (20) referred to symbolization as a structure-building, schematizing activity. Their argument is consistent with the notion that to depict an emotion, either representationally or symbolically, is not only a way of coming to know it but also a mechanism for developing a cognitive structure of it. This idea, that language is a means not only for representing experience (and, implicitly, its structure) but also for transforming experience, has been discussed by linguists and philosophers since it was first proposed by Herder more than 200 years ago (22). This thesis has received empirical support in recent years from ethnolinguistic research (23) on the Sapir-Whorf hypothesis (24), which states that the language of a culture determines the world view of people in that culture.

This perspective is taken a step farther, however, with the hypothesis that over time such symbolic activity generates a specifiable process of cognitive development. The general course of this developmental process was addressed in Werner's "orthogenetic principle of development" (25), which states that wherever development occurs it proceeds from a state of relative globality and lack of differentiation to a state of

increasing differentiation, articulation, and hierarchic integration (again, by implication, its structure). Although this perspective applies to cognitive development in the ontogenetic sense, cognitive activity at a given moment can be viewed as a construction that recapitulates the sequence of ontogenetic development. The phenomenon, called "microgenesis" or "aktual-genese," has been described by Werner (26, 27) and Draguns (28). This theoretical framework has been supported by empirical studies such as those using a tachistoscope, which have revealed that as the time of exposure increases the perception of a stimulus changes from being global and diffuse to being more differentiated and more integrated. Thus, our application of this point of view to the inner world of emotion suggests that emotional experience is constructed over time in both the ontogenetic and the microgenetic sense and that one's inner world can and does become known in the same way that the external world becomes known.

The next question to consider is the specific nature of this developmental process. Although much of the specific content of one's inner world must be assumed to be unique, the same holds true for the knowledge one has of the external world. This raises the question of whether the structural development of the knowledge one has of one's inner world might follow the sequence described by Piaget for cognitive development in general.

Piaget's theory of cognitive development is an attempt to describe the structural changes that take place over time in the organization of a child's knowledge of the external world. For Piaget, organization, structure, and schema are interchangeable terms (29). Schemata are the elements of cognitive structure that determine the nature of observable behavior, and schemata change during the course of cognitive development. Piaget described four major periods of cognitive development—the sensorimotor, preoperational, concrete operational, and formal operational periods. In general, these periods are characterized by a progressive trend toward abstraction and increasing coordination of the individual's schemata (30). Piaget focused on the organization or structure of knowledge rather than the specific content of the child's knowledge. Furthermore, he was not concerned with the emotional, social, and motivational factors that accounted for why a cognitive event occurred as it did at a particular time in a child's life, a concern which led Werner and Kaplan (20) to formulate their organismic-developmental viewpoint.

Empirical tests of Piaget's theory have produced mixed results. The concept that all of a child's cognitive functioning resides en bloc at a given stage appears to be incorrect (31). Numerous instances of a phenomenon known as horizontal decalage—the finding that cognitive skills in different task domains are organized at different levels of complexity in a given child—have been documented (32). The concept that cognitive skills develop in an invariant stepwise sequence has

also been challenged by the finding that more advanced skills in a given domain may appear before skills acquired earlier have been maximally developed (30). Furthermore, Piaget studied cognitive development only into late adolescence, although several theorists have proposed that a stage beyond the formal operational period may exist (33, 34). However, the levels of organization that Piaget described do appear to exist, and the sequence of development that he described does appear to apply to many specific domains of cognitive activity. Therefore, the structural transformations that Piaget described for knowledge about the external world may apply as well to the knowledge about the internal world of emotion.

Since Piaget himself did not view emotion as having structure, however, he did not address the topic very extensively: most of his thoughts about emotion are incidental comments in many of his writings, and his only extensive discussion of the topic was in a series of lectures at the Sorbonne in 1953–1954 (30). In general, Piaget viewed emotion as supplying the energetics of thought, while cognition provided the structure of thought. His view was that emotion in itself did not have structure but became structurally organized through intellectualization (35). However, Piaget was not particularly interested in how emotion influenced cognitive development, let alone in understanding emotion in its own right. His views on emotion were largely borrowed from the field of psychoanalysis, which itself has not proposed a unified theory of emotion (36, 37) or subjected its own concept of emotion as energy to rigorous empirical testing.

Greenspan (38) and Cowan (30) proposed that there are changes in the structure of emotional experience which occur in relation to Piaget's stages of cognitive development. These parallels were drawn in the context of attempts to integrate Piaget's theory with other aspects of personality development in childhood. Although these contributions have been extremely useful, they did not take into account the limitations of a purely Piagetian approach to cognitive development. Furthermore, a specific model of developmental changes in emotional experience independent of other realms of cognitive development was not presented. The latter is particularly important in the light of the clinical observation that highly intelligent individuals may be quite unsophisticated in their awareness of their own emotional reactions or those of others.

Nevertheless, there is one domain of cognitive activity directed toward the external world that is closely related to awareness of one's own inner emotional experience, namely, empathy. The link between the two domains derives from the hypothesis that the capacity to empathize with the emotional experience of others is thought to be based on the capacity first to imagine oneself in the other's situation and then to experience the emotional reaction one would have if one were in the position of the other in that situation (39, 40). Thus, empathy is an advanced cognitive skill that is based on the knowledge one has of one's own

TABLE 1. Five Levels of Structural Transformation of Knowledge About the External World and the Internal World

Level of Structural Transformation	External World	Internal World
Formal operational	Able to reason abstractly using hypotheticodeductive reasoning; able to consider all possibilities in a situation	Able to experience many nuances of emotion; own experience does not limit empathic awareness of other's experience
Concrete operational	Several attributes of an object integrated into unified concepts (e.g., conservation of volume), but reasoning based on immediate experience	Multifaceted emotional experience includes experiencing opposite feelings and blends of emotion as part of a single reaction
Preoperational	Has concept of individual attributes of objects that may be used idiosyncratically to represent the object as a whole	Has unidimensional, pervasive emotional reactions; emotional experience has an either/or quality
Sensorimotor (substages 2-6)	Learns about objects through handling and perceiving them	Able to induce a change in undifferentiated emotional state through actions on the environment
Sensorimotor (substage 1)	Has reflexive (involuntary motor) responses at interface with external world (e.g., sucking)	Has reflexive (involuntary motor) responses, both internally (autonomic, neuroendocrine) and at interface with environment (e.g., facial expression)

inner world. In view of the fact that behavior resembling adult empathy can be observed in young children and even infants (41), it is reasonable to consider that accurate empathy may represent the culmination of a continuum of ever-increasing awareness of another person's emotional experience. To the extent that this developmental process is an advanced application of the knowledge one has of one's own experience, the developing capacity for empathy may be a corollary of the developmental process described here.

FIVE LEVELS OF EMOTIONAL AWARENESS

The parallels between the structure of knowledge about the external world and the structure of knowledge about the internal world are illustrated in table 1. What defines the transition from one period to the next are transformations in the schemata for processing the incoming information: sensory data from the external world and emotional arousal from the internal world. Since these are different domains of knowledge, they may not be organized at the same level in a given individual.

Although Piaget focused on the course of ontogenetic development, Werner and Kaplan suggested that the different levels of organization may be used to describe momentary states as well as traits which characterize an individual's usual level of functioning. The term "stage," which Piaget used, is not as well suited to this dual interpretation as the term "level"; therefore, we have adopted the latter term. However, the concept that each level represents a hierarchical increase in differentiation and integration from the previous level incorporates both perspectives.

Piaget proposed that schemata are progressively revised through the twin processes of assimilation and accommodation. Assimilation means revising what is taken in to fit the schema, while accommodation refers to the adjustment of the schema to what is taken in (29). At early levels of organization the capacity for

assimilation is quite limited. Emotional information is primarily given out into the environment. Interventions from caretakers are needed to add new information that modifies the emotional experience and the schema for that experience. Over time the schemata that assimilate emotional arousal become more differentiated and integrated, so that more emotional information is processed internally. The individual gradually develops new ways of representing experience that are more flexible and can capture more of the information contained in the arousal. In this way the capacity to contain more of the arousal increases and the individual becomes more capable of regulating his or her own state without needing to rely so much on outside caretakers. Eventually the amount of information assimilated internally exceeds that conveyed to the environment, and the individual has much greater flexibility in determining the content of what will be shared with others and the circumstances in which this sharing will occur. The greater degree of organization of the inner world of emotion will be reflected in the structure of the verbal descriptions of emotion, however. As the capacity for self-regulation increases, the capacity to adapt successfully to a variety of environments improves.

An overview of the characteristics of the different levels of organization that characterize this process is presented in table 2. The first level of emotional awareness is sensorimotor reflexive (i.e., awareness of bodily sensations). At this level the involuntary motor phenomena that accompany emotional arousal are activated. These include autonomic and neuroendocrine changes as well as automatic facial expression. If there is conscious experience of emotion at this level, it is global arousal embodying the whole person and consists of bodily sensation only. The individual will report nothing or bodily sensation only. However, an outside observer could observe the individual's facial expression and begin to identify the quality of the emotion activated; i.e., emotional information is conveyed outward. Awareness of the separate existence of

TABLE 2. Characteristics of Five Levels of Emotional Awareness

Level of Emotional Awareness	Subjective Quality of Emotional Experience	Differentiation of Emotion	Ability to Describe Emotion
5. Formal operational	Peak differentiation and blending	Richer differentiations of quality and intensity	Description of more complex and differentiated states
4. Concrete operational	Differentiated, attenuated emotion	Blends of emotion, concurrence of opposing emotions	Description of differentiated emotions
3. Preoperational	Pervasive emotion	Either/or experience of emotional extremes (limited repertoire)	Description of unidimensional emotion
2. Sensorimotor enactive	Action tendency and/or global arousal	Action tendency or global hedonic state	Description of action tendencies or global hedonic states
1. Sensorimotor reflexive	Bodily sensation	Global undifferentiation of arousal	No description or description of bodily sensation

the other is minimal or nonexistent, and the awareness of the other's experience is itself reflexive.

The second level of emotional awareness is sensorimotor enactive (i.e., awareness of the body in action). At this level of structural transformation, emotion is experienced as both a bodily sensation and an action tendency, but the ability to experience emotion as a conscious feeling state has not yet developed. Action tendencies are based on global and all-consuming states of pleasure or displeasure that are aimed at maximizing pleasure and minimizing distress. The individual would describe action tendencies or global hedonic states, but the words used to convey the hedonic tone of the experience typically would not refer to emotion alone, e.g., "I feel bad." An outside observer could begin to identify the nature of emotional experience on the basis of voluntary and involuntary motor behavior. The awareness of the other as a separate individual is minimal, and the experience of the other is represented enactively through motor mimicry or the tendency to do things the way the other is doing them without being consciously aware that this is occurring.

The third level of emotional awareness is preoperational (i.e., awareness of individual feelings). At this level of structural transformation, representation of emotion is possible for the first time, and the quality of emotion changes such that it becomes a psychological as well as a somatic experience. Emotional states tend to be pervasive and have an "either/or" quality (e.g., either one is happy or one is sad), but the capacity to experience multiple emotions as part of a single emotional reaction has not yet developed. The range of emotions experienced is limited, and verbal descriptions of emotion are often stereotyped. The individual's capacity to experience emotion and yet modulate the amount of emotional information conveyed to the outside world is still quite limited. Other people are seen as different primarily on the basis of external characteristics such as height, race, gender, and age rather than internal characteristics such as feelings, values, and beliefs. The awareness of another person's

experience is idiosyncratic or inconsistent and is based on responding to a particular aspect of the other's behavior rather than multiple aspects of the behavior.

The fourth level of emotional awareness is concrete operational (i.e., awareness of blends of feelings). The range of emotional experience expands and now has more coherence, manifested by a greater appreciation of how emotional experiences can change over time and can supplement rather than supplant one another. At this level of structural transformation, emotional reactions become more complex in that they are composed of blends of emotions that are opposed to one another or closely differentiated from one another qualitatively or quantitatively. This capacity for more complex reactions is exemplified by a capacity to modulate emotional extremes, to experience hope when a situation may seem hopeless at a given moment, or to maintain an awareness of a variety of feelings for a person despite the immediate circumstances. The individual is able to describe complex and differentiated emotional states that capture his or her subjective experience. Representation in the enactive mode is much more selective because the individual can now anticipate how others may respond to a given course of action. Although others are now recognized as different on the basis of internal as well as external attributes, the appreciation of the other's emotional experience is unidimensional; i.e., it is relatively undifferentiated compared with one's awareness of one's own experience.

The fifth level of emotional awareness is formal operational (i.e., awareness of blends of blends of feelings). The major advance at this level of structural transformation is greater differentiation and integration in one's appreciation of the experience of others in the context of an ongoing differentiated awareness of one's own experience. There is now the capacity to mix or blend feelings of varying qualities and intensities into new patterns, even though such patterns have never been modeled or described by others. There is also the capacity to make subtle distinctions between nuances of emotion, and descriptions of such emotions

Acquisitions in Representation	Emotion Conveyed as Information	Self-Other Differentiation	Empathy
Novel representations (including metaphors)	Inward much more than outward	Advanced: recognition of integrated, separate identifies	Multifaceted awareness of other's state based on ability to imagine self in other's context
Advanced lexical	Inward more than outward	Recognition of many external and some internal differences	Attribution of experience based only on own perceptions and own experience
Imagistic and early lexical (stereotyped)	Outward more than inward	Recognition of differences mainly in external characteristics	Idiosyncratic or inconsistent awareness of other's experience
Enactive	Outward	Minimal	Motor mimicry, identification through behavior
Reflexive	Outward	Minimal or symbiotic	Reflexive empathy (e.g., crying when other cries)

may be novel or unique and include metaphors. It is now possible to perceive the differentiated, multidimensional experience of others unbiased by one's own emotional state, which includes the capacity to see a situation involving oneself through the eyes of others. The capacity to fully experience how one will feel at some future time under certain circumstances increases the likelihood that the decisions one makes in one's occupational or personal life will bring the satisfaction one is seeking. By anticipating the needs and reactions of others, one is better able to find courses of action that meet the needs of all involved. Self-other differentiation has reached its peak so that self and other are both recognized as unique as well as sharing universal characteristics.

IMPLICATIONS FOR THEORY, RESEARCH, AND PRACTICE

The cognitive-developmental model outlined here shifts the focus in the psychological domain from the quality and intensity of emotion to a more macroscopic perspective focusing on the organizational structure of emotional experience. These structural features include whether emotion is experienced as primarily a somatic state, a somatopsychic state (as in an action tendency), or a psychic state, as well as the degree of differentiation and integration of that experience. One major dividend of this theory is that it suggests new techniques for improving the assessment of conscious emotional experience. Since both the representation of the experience and the experience itself are hypothesized to arise from the same schemata, the structure of the representation should reflect the structure of the experience. The level of emotional awareness that an individual has reached can be assessed by presenting standardized emotion-evoking situations, asking the person how he or she would feel in each situation, and assigning a score to the responses based on the structural characteristics of the levels outlined in table 2 (unpublished paper of Lane et al.). The structural

assessment of conscious experience may provide an alternative to the clinical concepts of repression and other unconscious defense mechanisms that are extremely difficult to quantify. This approach may also make it possible to reappraise the longstanding findings that no consistent relationships can be found either between self-reported emotion and the biological indexes of emotional arousal or between social behavior and emotional experience (42).

Another benefit of this theory is that it provides a new perspective on the relationship between the different theories of emotion. To the extent that previous theories address the phenomenological component of emotion, the structural level of experience addressed in each theory provides the basis for categorizing them from a developmental perspective. For example, the James-Lange theory of emotion (43) holds that what we experience as emotion is the somatic activation present during emotional arousal. This can be understood to be a theory of emotion that emphasizes level 1 emotional experience. Darwin's theory of emotion (44)—that behavioral expression of emotion served an adaptive function for the organism—can be understood as a level 2 theory to the extent that it focuses on enactive representations of emotion rather than the experience of emotion in the usual sense of a feeling state. Plutchik (45) and Tomkins (46) have generated theories postulating that a limited number of primary emotions form the basis of all emotional experience, which corresponds to level 3 in our formulation, and Izard (47) and Ekman and Friesen (48), among others, have focused on blends of emotion, or level 4 experience. The fact that each theory could be presented in a persuasive fashion speaks for the coherence of each level of structural organization. It is important to recognize that the theory presented in this paper encompasses concepts from each of these other theories, just as each of the latter theories incorporates concepts from theories focusing on phenomena at lower levels of structural organization. To the extent that our formulation is empirically validated, it may form the basis for a new theory of emotion comprising

all three domains of emotion operating at all five levels. One of the implications of our model for such a theory is that the biological and social dimensions of emotion may each have levels of organization of function corresponding to each of the levels of emotional awareness (our unpublished paper).

Turning to more clinical applications, our cognitive-developmental continuum may have implications for selecting treatment modalities on the basis of the nature of a patient's level of emotional awareness. For example, individuals who manifest somatic symptoms (level 1 experience) such as neurovegetative symptoms of depression or motor restlessness require somatic interventions such as antidepressant medication or progressive muscle relaxation, respectively. Behavioral interventions such as operant conditioning, social skills training, physical restraint, or other limit-setting techniques may be most effective when overt behavior (level 2 experience) is seriously maladaptive and the capacity of the individual to reflect on the accompanying emotional state is negligible. Techniques such as cognitive-behavioral therapies may be most useful in individuals who manifest pervasive, unidimensional emotional experiences (level 3 experience) and need assistance in discriminating between affects, such as sadness and anger. Finally, individuals who consciously experience conflicts in their emotional states (level 4 and level 5 experience) may benefit most from insight-oriented psychotherapies. Obviously, sound clinical judgment is needed to determine at what level the individual usually functions, and multiple modalities may be needed depending on the nature of the problem and the goals of the treatment.

With regard to psychotherapy, our focus on the structural organization and transformation of emotion may also provide a new outlook on the process of change in psychotherapy. Stern (49) suggested that much of the work of psychotherapy consists of formulating experience for the first time as opposed to altering defensive processes that conceal fully formed mental contents residing in the unconscious. The process he described for experience in general may apply to emotional experience in particular and may follow the developmental sequence of levels of structural transformation outlined here. Since an individual may manifest considerable heterogeneity in his or her level of awareness in different areas of his or her life, this framework may help to identify areas of experience that are relatively underdeveloped and are in need of construction for the first time. The therapist can facilitate the process by offering verbal representations that have structural characteristics corresponding to the patient's current experience as well as by providing new labels and identifying previously unrecognized triggers of emotion, which can facilitate further structural development of emotional schemata. Since the model specifies the patient's level of awareness, it helps to identify the next step to be reached in therapy. Although the act of verbalization by the patient may actually intensify the patient's experience temporarily,

expansion of the schema through symbolic representation reduces the individual's vulnerability to future distress and disorganization, because future experience will be more differentiated, more attenuated, and more familiar by virtue of its being more integrated with the rest of one's emotional experience. This cognitive-developmental model may be used in the assessment of a patient during an initial evaluation, as a measure of outcome on the completion of treatment, and as a guide to trainees who are learning the skills necessary to become psychotherapists.

Perhaps the clinical entity that is addressed most directly by this theory is "alexithymia," a term coined in 1972 meaning "lacking words to express feeling" (50). In addition to having difficulty expressing feelings in words, patients with alexithymia have a paucity of fantasy life and describe the world in mechanistic terms (51). The concept of alexithymia arose in an attempt to capture how psychological factors contribute to the etiology, onset, and exacerbation of somatic pathology (52). Although several authors have suggested that this condition plays an important role in various somatic conditions, substance abuse (53), post-traumatic stress disorder (54), and other psychiatric conditions (55), there is controversy about whether the condition actually exists, and research has been hampered by the lack of an adequate operational measure of it (56).

Our theory sheds new light on the phenomenon of alexithymia in several important ways. On the basis of our formulation of emotional experience as an observer-dependent reality, we propose that the alexithymic individual, as currently described in the literature, is like the child from Florida confronted with a snowy landscape: the terrain is perceived and experienced as undifferentiated. The undifferentiated nature of emotional experience is self-perpetuating to the extent that the alexithymic individual avoids reflecting on and generating symbolic representations of experience. Our model suggests that an important reason for this avoidance is that unpleasant emotional arousal is experienced as overwhelming somatic distress when it is attended to.

This hypothesis is supported by the work of Linville (57), who has shown that individuals who manifest greater cognitive complexity in their descriptions of themselves are less likely to experience extreme perturbations in their emotional equilibrium than are those individuals who manifest lower levels of cognitive complexity. Furthermore, our theory suggests that the phenomenon is not a distinct entity but represents one pole of a developmental continuum: the inability to put feelings into words may be a global trait, a circumscribed trait pertaining to emotions of a particular type, or a transient state. Perhaps measures used to specify levels of emotional awareness may prove to be more precise measures of the concept of alexithymia and could be used to explore the many research questions generated by clinical observations in this area.

Since our developmental model goes beyond the concept of alexithymia by specifying the nature of emotional arousal when it cannot be put into words, it helps to define the nature of the emotional disturbance in those disorders in which alexithymia is thought to play a role. For example, although substance abuse disorders are not defined as being associated with a disturbance in emotional functioning, our developmental continuum suggests that substance abuse is a sensorimotor enactive response to relatively undifferentiated states of unpleasant emotional arousal (level 2). The nature of the emotional disturbance may be difficult to define clinically precisely because it is undifferentiated. Furthermore, consistent with the self-medication hypothesis of addictive disorders (58), our theory suggests that for substance-abusing patients certain types of emotional arousal (e.g., anger) are so overwhelming that pharmacological relief is the only remedy available to them. The clinical maxim that the substance abuse must stop before the motivational sources of the behavior can be identified and dealt with psychotherapeutically is entirely consistent with this theory. Our developmental continuum may also be useful in determining whether a deficit in emotional awareness related to substance abuse is present in someone who claims to use substances for recreational purposes only. Perhaps the extent to which impairments exist in the ability to put feelings into words either at the time of initial assessment or following short-term clinical intervention may be an important prognostic determinant of recovery from these disorders.

Another category of psychiatric disorders to which our cognitive-developmental approach may be applied is the affective disorders. Since the inception of *DSM-III*, it has become clear that considerable heterogeneity exists within a given diagnostic category with regard to response to treatment and course of the disorder. An example of this is the finding that the course of major depression is characterized by more frequent recurrences in patients with a concomitant dysthymic disorder, so-called double expression, than in individuals without a preexisting mental disorder (59). This observation may be understandable on the basis of a cognitive-developmental approach. Patients with dysthymic disorder have a range of emotional experience that is comparable to the emotional range of patients with major depression but is more constricted than the emotional range of individuals with no mental disorder. This suggests that individuals with no mental disorder have more developed emotional schemata and are less vulnerable to the pervasive emotional arousal of major depression than are individuals with dysthymic disorder. These considerations suggest that the baseline level of emotional functioning in a patient who develops an affective disorder interacts with and helps determine the cause of the affective disorder.

To the extent that this is true, a whole new group of clinical and research questions arise. For example, why don't all individuals at high genetic risk for affective

disorders develop episodes of such disorders? Do differences exist in the premorbid emotional functioning of those who develop an affective disorder and those who do not? What are the characteristics of the emotional experiences associated with the "precipitating event" leading to a first episode of illness or to relapse in a particular patient? Under what circumstances is insight-oriented psychotherapy a necessary adjunct to psychopharmacological management to prevent relapse, hospitalization, or suicide? It is quite possible that answers to these questions will lead to improvements in the prevention and treatment of these disorders.

A final category of psychiatric disorder to which our approach may be applied is schizophrenia. On the basis of Semrad's clinical observation that schizophrenic disorganization arises as a consequence of a failure to assimilate or "metabolize" unpleasant emotional arousal (60), one may hypothesize that the level of emotional awareness among schizophrenic patients would reflect this lack of assimilative capacity and be predictive of outcome to the extent that heterogeneity in level of emotional awareness exists among these patients. Although a direct test of this hypothesis has not yet been undertaken, Johnson and Quinlan's finding that nonparanoid schizophrenic patients have more fluid boundaries in their representations of human characters than do paranoid schizophrenic patients (61, 62) suggests that the level of emotional awareness in paranoid patients may be higher than it is in nonparanoid patients. This in turn may help to account for the observation that both short-term and long-term outcomes are better in paranoid than in nonparanoid patients (63). To the extent that this use of our cognitive-developmental model is valid, the model may provide a new framework for integrating other, seemingly disparate, findings regarding the association between emotion and outcome in schizophrenia, such as the finding that schizophrenic patients with depressive symptoms have better outcomes (64) and that high expressed emotion (open criticism, hostility, and affective overinvolvement) in families of schizophrenic patients is associated with poorer outcome (65, 66).

In summary, this discussion shows that when one adopts a cognitive-developmental approach to emotion and emotional awareness, one's thinking becomes more differentiated and integrated with regard to a number of different issues: the objective measurement of emotional experience, theories of emotion, strategies of clinical intervention, the process of change in psychotherapy, the phenomenon of alexithymia, the etiology of substance abuse, and the heterogeneity of outcome among patients with affective disorders and schizophrenia. Although we have not discussed them in this paper, this framework has a similar influence with regard to other areas of psychopathology as well as our understanding of phenomena related to the biological and social domains of emotion (our unpublished paper). An important test of the usefulness of this perspective will be the extent to which instruments

such as the Levels of Emotional Awareness Scale (unpublished paper of Lane et al.) that are specifically designed for the objective measurement of levels of emotional awareness facilitate empirical investigation of the questions outlined in this paper.

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Temperament and Intellectual Development: A Longitudinal Study From Infancy to Four Years

Michel Maziade, M.D., Robert Côté, Ph.D., Pierrette Boutin, M.Ps.,
Hugues Bernier, M.Ss., and Jacques Thivierge, M.D.

Using three temperamentally different subgroups from a large birth cohort, the authors undertook a longitudinal study of the association between temperament measured in children at 4 and 8 months and IQ assessed at 4.7 years. The data suggested a strong effect of extreme temperament traits on IQ development in middle and upper socioeconomic classes and in families with superior functioning in terms of communication. The temperamentally difficult group unexpectedly displayed higher IQs, and the well-replicated effect of socioeconomic status on IQ development was observed mainly in this group. These data support the hypothesis that difficult infants activate special family resources, which stimulates intellectual development over the years.

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Temperament and intelligence are concepts that have profoundly marked the evolution of developmental and clinical child psychiatry and psychology. What IQ has been to our understanding of cognition, temperament is becoming to our comprehension of

personality development. This profound influence probably stems from the fact that, unlike many concepts widely used in the behavioral field, the concepts of temperament and IQ have been and still are based on results of methodical investigations, thus keeping behind, instead of ahead of, the facts.

In addition to the child temperament model derived from the New York Longitudinal Studies (NYLS) (1), different operational definitions of temperament have been developed to which many conclusions may be empirically attached (2–4). Evidence exists that temperament is influenced by genes (5, 6) and that this influence increases with age (3). Temperament has not been associated with socioeconomic status in cross-sectional studies (7, 8) or with the type of delivery procedures or perinatal events (9). Patterns of continuity and change of temperament seem genetically modulated (10) and associated with family variables (11). An aggregation of traits resembling the NYLS “easy-difficult” typology has been replicated transculturally and at diverse age levels in our population (7, 8) and elsewhere. Moreover, the predictive value of this typology in interaction with family variables has been evidenced in our French-speaking population (12). We have previously discussed the pros and cons of temperament perceived through parental questionnaires versus temperament observed in an unusual laboratory environment (13). Although many conceptual and measurement issues remain to be clarified, child temperament is now regarded as an important variable in human development (14, 15).

Although Vernon (16) wrote in 1965 that intelligence is not a definite entity but “depends upon personality and motivational factors, organic and social drives, curiosity and interests,” little is still known about the developmental interplay between personality variables and intellectual abilities (17). Marked individual changes in mental test performance during

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infancy and preschool years are observable but still unexplained. While intelligence can assuredly not be determined by IQ measurement alone, IQ is so far a well-documented and practical way to apprehend intellectual abilities (18).

Many well-replicated characteristics apply to children's IQs. First, IQ, like temperament, displays some genetic as well as environmental influences (19, 20). Second, in terms of predictive validity, very low IQ predicts future low achievement; however, smaller although noticeable variations around the mean (15–20 points) display inconsistent relationships with future scholastic or social achievement, indicating that other intrinsic or environmental factors interact with IQ and influence such achievement. Third, socioeconomic status is associated with IQ (17, 21, 22); by itself, parental socioeconomic status is not the influential variable, but there is an indication that upper-class parents stimulate their children differently than lower-class parents (23). The well-replicated association of family size and child rank with IQ level is probably also mediated by differences in the type of verbal communication and other stimulation provided by the parents (20, 24–26). Fourth, epidemiological data reveal that low IQ may be a risk factor for psychiatric and antisocial disorders and that high IQ may be a protective factor against adversity (27, 28).

Clearly, the study of the interplay between temperament, IQ, and family variables in infancy and preschool years is relevant developmentally to throw light on the intricate interactions between environment and specific child qualities. The investigation of such interactional patterns is also of epidemiological and clinical importance, since temperament and IQ may also be studied as risk and protective factors and thus help us to understand the future appearance of disorders.

In this study, we assessed the relationship between extreme traits of temperament in infancy and intellectual development in preschool years and also took into account the effect of socioeconomic status and certain aspects of family functioning. We were able to control for the effect of family size and the child's rank in the family.

We selected two specific dimensions of family functioning and used the McMaster Model of Family Functioning (MMFF), previously found reliable (12). Parental behavior control measured on the MMFF had previously been found to interact with temperament in middle childhood to predict later behavior disorders (12) and seemed associated with continuity and change of temperament (11). Parental control has also been found to be associated with children's competence in preschool years (29). The MMFF measure of behavior control assesses the clarity of family rules, the consensus between parents about rules, and parental consistency when rules are violated by children (30). We also assessed the MMFF communication dimension, which taps the quantity and quality of communication as well as the clarity and appropriate direction of instrumental and affective messages and found both dimen-

sions to be independent of socioeconomic status ($r=.11$, $p=.25$, and $r=.12$, $p=.30$; unpublished paper).

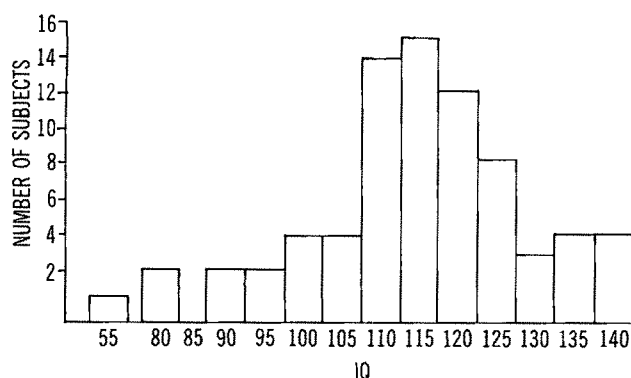
METHOD

We selected three subgroups of infants from our 1979 birth cohort ($N=358$). This initial sampling consisted of all babies born in a catchment district within a specific period as officially reported to a community health department of Quebec City (7). The infants were assessed at 4 and at 8 months by means of a French translation of the Carey et al. infant temperament questionnaire (31), which is based on the nine NYLS categories of temperament. We characterized all the infants on our bipolar factor I (principal component analysis), whose stability in infancy and at age 7 and whose similarity with the NYLS easy-difficult typology have been discussed (7). Five traits loaded strongly on factor 1: adaptability, approach/withdrawal, intensity, mood, and distractibility.

The first subgroup of infants displayed extreme traits on the difficult end of the continuum (above the 70th centile on the factor scores distribution) at both the 4- and 8-month measurements. A second subgroup of easiest temperament was composed of infants under the 30th centile on factor 1 at the two occasions. A third subgroup of average temperament consisted of infants situated between the 30th and the 70th centile at both occasions.

The three subgroups were matched for sex and socioeconomic status, which resulted in a total of 29 infants in each subgroup. The selection was made by using research codes; the investigators and parents remained blind to the infant temperament scores. The parents of 80 subjects (92%) agreed to participate. The mean age \pm SD of the children at time of follow-up was 4.7 ± 0.10 years; 62% were boys. The socioeconomic statuses (32) for this sample were as follows: classes I and II, 8%; class III, 19%; class IV, 33%; and class V, 40%. There were no significant differences between subgroups in terms of family size, child rank, and maternal depression index (Zung scale).

Temperament was reassessed at age 4.7 by means of a translated Thomas and Chess Parent Temperament Questionnaire (1), which is also based on the NYLS nine categories. The reliability, structure, and demographic characteristics of this questionnaire have been reported (8). When the subjects were 4.5 years old, a first home visit was made to give explanations and obtain a signed consent. Then two other independent home visits permitted 1) an intellectual assessment of the child by means of the Wechsler Preschool and Primary Scale of Intelligence (33) administered by a psychologist (P.B.) and 2) a family assessment through the McMaster's semistructured interview conducted by an experienced investigator (H.B. or J.T.), who then rated behavior control with the McMaster 7-point scale (a global rating and separate ratings for consensus rules clarity, and consistency) and communication

FIGURE 1. Score Distribution of the Wechsler Preschool and Primary Scale of Intelligence Full Scale IQ for 75 4.7-Year-Old Children

(a global rating and separate ratings for instrumental and affective communication). At the time of psychometric assessment, two subjects could not be visited for evaluation because of travel difficulties. As a result of their resistance and lack of cooperation, two other subjects (one of difficult and the other of average temperament when infants) were only assessed with the performance scale, and a third (difficult as an infant) could not be assessed either with the performance scale or the verbal scale; these three subjects did not appear to suffer from any clinical disorder or developmental delay. This reduced the total number of subjects to 77 (88.5%) for the performance IQ and to 75 (86%) for the verbal IQ and full scale IQ. The family interview was audiotaped, independently reviewed, and rated by another investigator, and yielded a satisfactory interrater reliability ($r=.79$ for behavior control and $r=.85$ for communication).

With respect to the Wechsler and other standardized developmental indexes, evidence suggests that the norms might be somewhat outdated (34–37), possibly because of the more diverse stimuli available to children during the last decades and the recent social trend toward smaller family size, which is associated with higher IQ. In spite of this, we used the Wechsler to allow comparisons with future assessments in this longitudinal study. In our sample, the score distribution presented in figure 1 is almost symmetric; as expected, we observed a shift of the curve to the right by around 15 points, but we believe this does not preclude comparisons for our three subgroups, given that they were assessed on the same basis.

RESULTS

To look at the association between infant temperament and IQ at age 4.7 years, we first performed Spearman rank correlations on the whole sample. This yielded only $-.15$ ($p=.19$) for the verbal IQ, $-.22$ ($p=.06$) for the performance IQ, and $-.23$ ($p=.04$) for the full scale IQ.

TABLE 1. Correlation Between Infant Temperament and IQ at 4.7 Years in Each Socioeconomic Status Category and Family Functional Level

Subgroup	N	Spearman Rank Correlation (r_s)		
		Verbal IQ ^a	Performance IQ ^b	Full Scale IQ ^c
Total sample	75	-.15	-.22	-.23 ^d
Social class				
Hollingshead I, II, III	21	-.52 ^d	-.31	-.48 ^d
Hollingshead IV	26	-.08	-.19	-.25
Hollingshead V	28	.12	-.15	.02
Family communication ^e				
Dysfunctional (MMFF score<4)	19	.13	.17	.24
Average (MMFF score=4)	16	.19	-.21	-.30
Superior (MMFF score>4)	27	-.50 ^f	-.60 ^g	-.66 ^g
Family behavior control				
Dysfunctional (MMFF score<4)	20	-.15	-.14	-.14
Average (MMFF score=4)	17	-.12	.01	-.15
Superior (MMFF score>4)	38	-.11	-.37 ^d	-.34 ^d

^aSignificant difference between the correlations for Hollingshead I, II, and III and Hollingshead V ($p=.01$) and for dysfunctional family communication and superior family communication ($p=.02$) (Fisher's transformation test).

^bSignificant difference between the correlations for dysfunctional family communication and superior family communication ($p=.003$, Fisher's transformation test).

^cSignificant difference between the correlations for Hollingshead I, II, and III and Hollingshead V ($p=.04$) and for dysfunctional family communication and superior family communication ($p=.001$) (Fisher's transformation test).

^d $p<.05$.

^eSingle-parent families ($N=13$) were excluded because it is impossible to assess adequately MMFF communication in such young families when one parent is absent.

^f $p<.01$.

^g $p<.001$.

Because of variance heterogeneity, it was not appropriate to test through an analysis of variance (ANOVA) the possible interactions between temperament and other independent variables. However, we looked at the correlation between temperament and IQ within each socioeconomic status category (table 1). Hollingshead classes I, II, and III were grouped together because of the small numbers in the upper classes. We observed a significant association of temperament with IQ in middle and upper socioeconomic status only ($r_s=-.48$, $p<.05$; the negative sign indicates that difficult infants have higher IQs). We also looked at the relationship between socioeconomic status and IQ in each temperament group as well as in the whole sample (table 2). As replicated in many studies, an overall socioeconomic status effect in the total sample ($r_s=-.34$, $p<.01$) was observed, but strikingly, socioeconomic status showed its strongest effect in the difficult group ($r_s=-.71$, $p<.005$). To test the differences between the correlations found in the different subgroups, Fisher's transformation tests were performed (tables 1 and 2).

We also looked at family communication and family behavior control as control variables (table 1). We

TABLE 2. Correlations Between Socioeconomic Status and IQ at 4.7 Years in Each Infant Temperament Group

Infant Temperament Group	N	Spearman Rank Correlation (r_s)		
		Verbal IQ ^a	Performance IQ ^b	Full Scale IQ ^c
Total sample	75	-.27 ^d	-.33 ^e	-.34 ^e
Difficult	23	-.62 ^f	-.54 ^e	-.71 ^f
Average	26	.04	-.03	-.06
Easy	26	-.13	-.34	-.25

^aSignificant difference between the correlations for difficult and average infants ($p=.01$) and for difficult and easy infants ($p=.03$) (Fisher's transformation test).

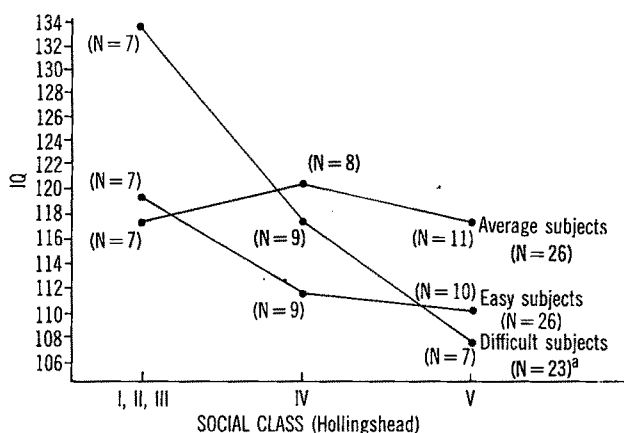
^bSignificant difference between the correlations for difficult and average infants ($p=.03$, Fisher's transformation test).

^cSignificant difference between the correlations for difficult and average infants ($p=.003$) and for difficult and easy infants ($p=.02$) (Fisher's transformation test).

^d $p<.05$.

^e $p<.01$.

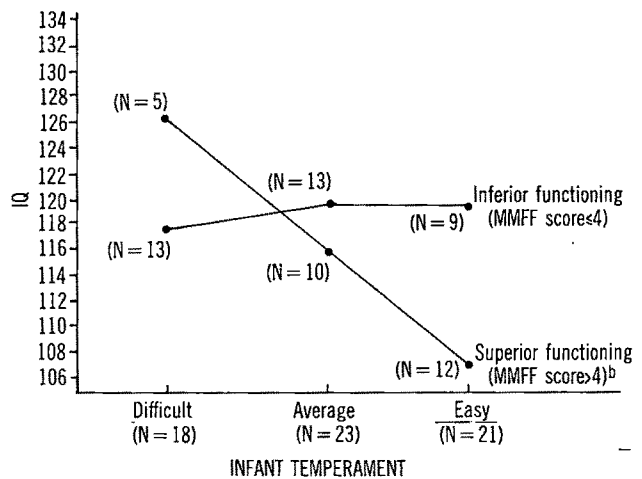
^f $p<.005$.

FIGURE 2. Effect of Socioeconomic Status on IQ for Each Infant Temperament Group

^aFor the difficult group, the mean IQ was significantly higher in Hollingshead classes I, II, and III than in Hollingshead class V ($t=3.94$, $df=8$, $p<.005$; Bonferroni correction, $p<.05$).

observed that infant temperament and IQ at age 4.7 years (both verbal and performance) were significantly correlated in families with superior levels of communication (MMFF score >4) and furthermore that difficult infants showed a strikingly higher IQ in this type of family. The behavior control dimension showed less effect on the association between temperament and IQ. To some degree, figures 2 and 3 also suggest an interaction of temperament with socioeconomic status and with family communication. The Brown-Forsythe statistic does not point out definite statistical interactions ($p=.09$), but a robust regression approach (38) suggests the presence of such interactions.

We also studied the relationship between temperament assessed at 4.7 years and IQ. First a principal component analysis was run on the temperament mean category scores assessed at 4.7 years: we again found

FIGURE 3. Effect of Infant Temperament on IQ With Respect to Level of Family Communication^a

^aSingle-parent families ($N=13$) were excluded because it is impossible to assess adequately MMFF communication in such young families when one parent is absent.

^bIn families with superior levels of communication, the mean IQ of the difficult infants was significantly higher than that of the easy infants ($t=4.34$, $df=8$, $p<.002$; Bonferroni correction, $p<.05$).

at that age the same five categories strongly loading on factor 1 as in infancy (7) and at age 7 (8). Each subject could then be characterized by a factor score on factor 1 at age 4.7 years. The correlations between this difficult-easy factor score and IQ were nonsignificant ($r\leq.10$). Of the nine temperament categories assessed at 4.7 years, only two (sensory threshold and persistence) correlated with IQ ($r=-.45$ and $r=.32$, respectively). When we looked at the correlations in middle and upper classes, or in families with superior communication, the results were similar.

DISCUSSION

Although extreme infant temperament alone showed little or no main effect on IQ, we found a significant association between infant temperament and IQ assessed at 4.7 years when we took into account social class or certain aspects of family functioning. If we consider that we have an index of the behavioral style of young infants, the magnitude of the association found in upper and middle classes and in families with a superior level of communication is striking: the correlations are in the .50-.60 range, especially for verbal IQ, while the IQ mean differences between groups are more than 20 points. Unexpectedly, difficult infants showed a higher IQ.

How can difficult infant temperament be an advantage with respect to intellectual development? It might be that less adaptable infants, withdrawing from new stimuli, intense in their emotional reactions, not distractible (not soothable), and negative in mood, solicit to a greater degree the interactions and opportunities

available from a certain category of parents. In order to quiet the child or to mold the child's style to make it more desirable, parents would pay greater attention, talk more, or interact more. Such parents would stimulate the difficult infant more than the extremely easy infant, who is more readily left to himself. Such special stimulation would favor more rapid development.

This interactional hypothesis may partially explain why temperament is associated with IQ only in upper- and middle-class families: because upper-class parents are different from lower-class parents in their manner of stimulating children. Some studies have indicated that upper- and middle-class parents provide more stimulation, especially linguistic stimulation (20, 26, 39–42). Further, empirical data strongly suggest that differences in linguistic environment have links with children's intellectual development, even though the mechanism of influence remains to be clarified (23, 43–45).

Conversely, socioeconomic status showed its strongest effect on IQ in the difficult infant group. The well-demonstrated association of socioeconomic status with IQ is thus distributed in our sample not equally but differentially, according to the child's temperamental style. Extreme temperament traits possibly provoke and bring to light the observable differences in parental stimulation between upper and middle classes and lower classes, the children with difficult temperament soliciting more of this environmental potentiality, which exists predominantly in upper- and middle-class parents. This indirectly supports the view that the social class effect on the children's intellectual development is mediated in part by the quality and quantity of the stimulation provided.

We also found that difficult infants tended to have higher IQs at age 4.7 years mainly in the families with a superior level of communication. By demanding more attention, difficult children would provoke more interaction available in families with superior communication and thus benefit from the additional stimulation, which speeds up their intellectual development. Since such an opportunity is lacking in other families, the individual differences of temperament would not influence intellectual development. This is compatible with our previous hypothesis that an environment which provides opportunities for stimulation and communication is an important element in the interaction with temperament and IQ.

In addition, our data indicate that temperament has differential interplay with family environment. Temperament seems to interact less with family behavior control ($r = -.34$) to bring about a significant difference in IQ than with communication ($r = -.66$), which suggests that appropriate environmental stimulation interacts to a greater extent with temperament to influence development than optimal qualities of behavior control. This result is congruent with previous studies showing an association between IQ change and parental control (46, 47) and suggesting that the early

influence on IQ change from the availability of stimulation is greater than that from parental control (48).

Our finding that temperament assessed at 4.7 years correlates little or not at all with IQ at the same age suggests that the cumulative effect of the interaction between early temperament and family variables, built up over several years, has a greater influence on intellectual development than the temperament traits directly observable at the moment of the test. Our data also eliminate the possibility that temperament at 4.7 years influenced importantly the IQ measurement itself.

Some studies (49–51) reported no association between temperament and developmental indexes such as the Bayley in the first 2 years of life. Our results from infancy to 4.7 years are somewhat discrepant with these results. Developmental and methodological reasons might explain this discrepancy. First, these other studies, conducted earlier in the child's life, may have found no association because the progressive and cumulative interactional effect between temperament and environment may take several years to produce a measurable effect on development. Our finding of a strong association between infant temperament and IQ is inconsistent with the results and conclusions of Daniels et al. (49), who found no association between infant temperament and the Bayley scores at 12 and 24 months or any interactional effect. They concluded that their data were adding "growing doubts about the utility of the construct of difficult temperament." We believe that, at the present state of empirical knowledge, such a strong conclusion was premature, especially since their measurement of the NYLS temperament consisted only of a parent's "general impression" scale, which asked only one global question about each temperament trait. Such global impression correlates rather weakly with the multiple items of the infant temperament questionnaire in American samples (31) and in ours and shows less stability from 1 to 3 years than the infant temperament questionnaire (52). Their measurement of temperament and its possible weak validity and specificity may explain their not detecting possible significant associations with various parameters. Daniels et al. (49) and Vaughn et al. (51), in their analyses, did not take into account social class, which presented a strong differential effect in our study, and Bates et al. (50) found little or no interaction of socioeconomic status in their multiple comparisons with fussiness—"difficultness." Considerations about the use of different samplings and their consequences on socioeconomic status representativity may partly explain our different results. Our initial random sample from the general population, which was representative of all socioeconomic statuses, as well as the similar social class representativity of our subsample, may better reflect the full range of the socioeconomic variability of the general population; such a sampling increases the chances of including the two extremes of the socioeconomic continuum of a population and consequently of finding significant social class varia-

tions. In addition to the sampling, our satisfactory (although imperfect) rate of response for the initial sample (78%) and for the subsample (86%) tends to diminish a possible bias linked with the use of solicited and volunteer samples or with the fact that a large number of families refuse to collaborate in the process of accumulating subjects for longitudinal studies. Indeed, nonrespondents are different from respondents in epidemiological (53, 54) and clinical (55, 56) studies, and it is probable that volunteers and families willing to participate in a longitudinal study are different from unwilling families with respect to many parental, personal, and social characteristics that may influence the effect on the dependent variables. Our rate of respondents and our selecting extreme subjects from a population-based random sample may partly explain why our results are striking in comparison with results from other studies in which other procedures were used.

We selected the two extremes of the temperament continuum and an average group. Our criteria for difficultness and easiness apply respectively to around 15% of the most difficult and easiest infants in our population. However, we believe that the restriction of not being able to generalize to the whole population (57) is compensated for by the fact that in preventive and clinical settings we face the extreme cases in a population. In addition, our previous data on extreme subjects (12, 58) and the present results support the view that studying extreme subjects may uncover consistent relationships that cannot be detected with around average subjects. Exploratory work on extreme characteristics, either intrinsic or environmental, is less costly because it allows for the use of smaller sample size, an important advantage given the present economic restraints on research funding. The study of extremes complements the studies of variations on the whole continuum. Important new deductive hypotheses for consecutive research might be derived from observations of similarities and dissimilarities in findings between extreme and average subjects.

We must keep in mind that our results are derived from small subsamples and thus need further replication. However, they suggest a strong interplay from infancy to preschool years between extreme temperament and IQ, provided that specific environmental opportunities are present. This interplay may to some degree explain why studies of developmental indexes measured under the age of 18 months (18, 20, 59), without consideration of temperamental differences, show no relation to IQ measured in later years. Our data also support the already expressed hypothesis that the very idiosyncratic patterns of IQ evolution observed for any individual (17, 47) may partially originate from individual temperament differences (20). We cannot eliminate the possibility that our findings could be explained by an intrinsic constitutional link between temperament and IQ; however, at the present state of empirical knowledge, we believe that any constitutional hypothesis is unwarranted.

Finally, our present longitudinal data suggest that the extreme temperament traits of difficultness, even if considered undesirable at one time of a child's life, may present advantages at another. The present findings and the emphasis of Thomas and Chess (1) that even extreme temperament traits are not equivalent to deviancy but just one of many aspects of normal human variability help us to keep in mind that in no way do undesirable temperament traits reflect a weakness in the constitutional basis of personality.

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Phenomenological Correlates of Metabolic Activity in 18 Patients With Chronic Schizophrenia

Nora D. Volkow, M.D., Alfred P. Wolf, Ph.D., Peter Van Gelder, Ph.D.,
Jonathan D. Brodie, M.D., John E. Overall, Ph.D.,
Robert Cancro, M.D., and Francisco Gomez-Mont, M.D.

Using [^{11}C]-deoxy-D-glucose and positron emission tomography (PET), the authors measured brain metabolism in 18 patients with chronic schizophrenia to assess which of the metabolic measures from two test conditions was more closely related to the patients' differing clinical characteristics. The two conditions were resting and activation, and an eye tracking task was used. Patients with more negative symptoms showed lower global metabolic rates and more severe hypofrontality than did the patients with fewer negative symptoms. Differences among the patients were distinguished by the task: sicker patients failed to show a metabolic activation response. These findings suggest that cerebral metabolic patterns reflect clinical characteristics of schizophrenic patients.

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Schizophrenia has been categorized as a heterogeneous disorder (1). Among the several phenomenological classifications that have been proposed, one is based on the distinction between those patients having positive symptoms (hallucinations, delusions, bizarre behavior, and thinking disorder) and those patients displaying negative symptoms (blunted affect, emotional withdrawal, poverty of thought, and anhedonia) (2). These two symptom complexes have been associated with different therapeutic and prognostic out-

comes. Positive symptoms are likely to be correlated with better premorbid adjustment, better response to neuroleptics, and a less malignant course. On the other hand, negative symptoms are associated with poor treatment response, cognitive impairment, and CAT scan abnormalities (3-6).

Different underlying pathological processes have been implicated for each type. The negative presentation has been related to a more residual deficit state and has been associated with lower dopamine activity. In contrast, the positive symptom pattern has been associated with higher density of dopamine receptors or, possibly, with a decrease in inhibitory mechanisms in the brain (7).

The purpose of this study was to evaluate whether different patterns of regional brain metabolic activity distinguish schizophrenic patients with different clinical characteristics. Positron emission tomography (PET) was used to measure cerebral metabolism of glucose, which has been shown to reflect brain function (8). Previous studies have reported abnormal metabolism in the frontal cortex of some schizophrenic subjects. In this study, we compared the cerebral patterns of glucose metabolism associated with a baseline state and with activation by an eye tracking task in a group of chronic schizophrenic patients distinguished by their varying predominance of negative and/or positive symptoms. We selected a smooth pursuit eye tracking task because it has been shown to be impaired in a large percent of schizophrenic patients (9) and because this impairment is associated with dysfunction of the frontal cortex (10). We hypothesized that activation of a deranged cerebral system would accentuate the differences between normal and dysfunctional cerebral systems.

METHOD

The control group consisted of 12 normal right-handed male volunteers (average age, 29 years). The patient group consisted of 18 right-handed men who fulfilled both *DSM-III* criteria and Research Diagnostic Criteria (RDC) (11) for chronic schizophrenia. Only patients with concordant diagnoses made by two

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psychiatrists using a structured interview (the Schedule for Affective Disorders and Schizophrenia [SADS] [12]) were included in the study. A Brief Psychiatric Rating Scale (BPRS-18) (13) was completed by one of the evaluating psychiatrists at the time of each patient's entry into the study.

All patients were receiving neuroleptic medication as well as anticholinergic medication for extrapyramidal effects of neuroleptics at the time of the study. Subjects were investigated after clinical stabilization was achieved. Twelve were in the last phases of their hospitalization, and six had been discharged within 1 week of completion of the study.

Presence of negative and positive symptoms was assessed according to the symptom definitions of Andreasen (14) by using both the psychiatric interview and chart review data. Expression of positive symptoms was scaled from 0 to 4 by adding the values for hallucinations, delusions, positive formal thought disorder, and bizarre behavior (each rated 1 for presence or 0 for absence) and from 0 to 5 for negative symptoms by adding the values for affective flattening, alogia, avolition, anhedonia, and attentional impairment (each rated 1 for presence or 0 for absence). Because the distinction between positive and negative symptom presentation is not a pure one (many patients show some combination of positive and negative symptoms at the same time), we classified the patients into two subgroups on the basis of predominance of negative symptoms (15). Patients with scores of 4 or 5 in the negative symptom dimension were classified as having predominantly negative symptoms and were differentiated from the other patients, who were described as having predominantly positive symptoms. Demographic and clinical characteristics of the patients are presented in table 1. Informed consent was obtained from all subjects after adequate description of the procedure.

Glucose metabolism was assessed by using a venous bolus injection of 7–15 mCi of 2- ^{11}C -deoxy-D-glucose as the tracer. Scanning and image reconstruction were done according to standard procedure (16). Each subject had two injections 3 hours apart. Scanning was started 40 minutes after injection of the label on the PETT VI (resolution full width half maximum [FWHM] of 11.8 mm in the plane of section). The first procedure was done under baseline conditions (eyes open, ears plugged) with the subject resting on the PET table in a dimly lighted room with minimal noise. For the second procedure, subjects were asked to concentrate on a visual task throughout the first 35 minutes of the glucose uptake period. The task was displayed on a video screen and was a randomly generated shape with 8 vertexes changing randomly every second to a different shape among 40 alternatives. The stimulus moved horizontally in a pendular fashion. Subjects were instructed to respond with a right foot twitch if the shape was the same as the one immediately preceding, except vertically reversed, as a monitoring task.

Fourteen overlapping metabolic images separated by 7 mm on centers and parallel to the canthomeatal plane were obtained from each subject for each PET scan. The two upper slices and two lower ones were excluded from the analyses because of the partial volume effects of contiguous bone.

Each slice was divided into regions representing distinct anatomical areas delineated by using a standard neuroanatomical atlas (17) and the individual CAT scan. Estimates of metabolic activity of whole cortical lobes for left and right hemispheres were obtained by averaging the pixels from the different slices that corresponded to the same anatomical region. We were interested in obtaining large topographic areas to reduce the error from partial volume effect (18) and the imprecision of obtaining a value from a region that could vary in its location in the Z axis. We obtained an estimate for the metabolic activity of the whole brain gray matter by averaging the values from the pixels of cortical and subcortical gray matter for all the slices.

Absolute metabolic measures were obtained for whole brain gray matter and for left and right frontal, parietal, temporal, and occipital lobes. Because the large variation in whole brain metabolic activity tends to mask regional pattern effects, the absolute values were next transformed into relative values. Relative values were obtained by dividing the activity in each brain region by the value for the whole brain gray matter. This set of measures was obtained for both the images taken during the baseline condition and those taken during the task. To assess regional differences between the normal subjects and the schizophrenic patients as a whole, we conducted univariate analyses of variance (ANOVAs) on the absolute and the relative metabolic values for the baseline condition and the task condition separately as well as combined. A two-way ANOVA was used to test the significance of effects associated with positive versus negative symptom classification across both baseline and task conditions (main effect) as well as the Task by Symptom Type interaction.

The relation between the regional metabolism and the clinical characteristics of the patients was analyzed by using three different strategies. First, the schizophrenic patients were classified according to symptom type into those with predominantly negative and those with predominantly positive symptoms. Differences in absolute and relative regional cerebral metabolism between these two groups for the baseline and for the task condition were tested for significance by using univariate ANOVAs. To assess differences in the magnitude of effect of the visual task on the relative metabolic values in the two groups of patients, the Baseline/Task by Symptom Classification interaction was tested in a two-way repeated-measures ANOVA. The second type of analysis approached the positive versus negative distinction as dimensional rather than as categorical. In this analysis, the correlations between the regional glucose metabolism and the nega-

TABLE 1. Clinical Variables of Patients With Chronic Schizophrenia Who Had Predominantly Positive (N=8) or Negative (N=10) Symptoms

Clinical Variable	Patients With Positive Symptoms										Patients With Negative Symptoms										Mean	SD
	1	2	3	4	5	6	7	8	Mean	SD	9	10	11	12	13	14	15	16	17	18		
Age (years)	22	36	28	23	21	25	27	20	25.00	5.00	31	30	30	20	39	27	32	41	31	39	32.00	6.00
Duration of illness (years)	3	7	5	4	3	7	6	5	5.00	1.80	4	12	9	6	4	8	15	20	4	10	9.10	5.13
Number of positive symptoms	3	3	4	3	3	3	2	2	2.90	6.00	4	2	2	4	3	2	2	2	2	2	2.40	7.00
Number of negative symptoms	2	3	3	2	2	3	3	3	2.60	0.50	4	4	5	4	4	4	4	4	4	5	4.20	0.40
BPRS score																						
Somatic preoccupation	1	4	4	2	1	3	1	1	2.13	1.27	2	1	3	3	1	1	2	3	1	1	1.80	0.87
Anxiety	1	4	3	3	3	4	2	2	2.75	0.37	2	4	4	4	3	4	5	3	4	5	3.80	0.87
Emotional withdrawal	2	3	3	1	2	2	4	2	2.38	0.86	6	3	5	4	2	2	4	1	4	4	3.50	1.43
Conceptual disorganization	3	3	4	3	3	2	2	3	2.88	0.60	5	3	4	3	4	4	4	4	3	4	3.80	0.60
Guilt feelings	1	1	1	1	1	1	1	1	7.00	0.00	2	3	1	1	1	1	1	2	3	1	1.60	0.80
Tension	1	4	3	3	3	4	1	1	2.50	1.22	1	3	3	3	3	4	5	3	5	5	3.50	1.20
Mannerisms	1	2	3	2	4	2	1	2	2.13	0.93	3	2	2	2	3	1	3	3	3	5	2.70	1.00
Grandiosity	2	2	2	4	1	1	3	1	2.00	1.00	2	2	1	1	1	3	1	3	1	1	1.60	0.80
Depressive mood	1	2	1	1	1	3	1	1	1.38	0.70	3	1	2	5	2	3	2	1	3	4	2.60	1.20
Hostility	1	3	1	3	5	4	1	2	2.50	1.41	2	2	4	3	2	4	5	2	1	1	2.60	1.28
Suspiciousness	2	5	5	4	5	2	1	2	3.25	1.56	2	5	5	4	5	4	5	3	3	5	4.10	1.04
Hallucinations	1	4	3	2	1	4	4	3	2.75	1.20	6	2	5	4	4	4	3	4	1	4	3.70	1.35
Motor retardation	1	1	2	1	1	1	2	2	1.38	0.48	2	1	6	1	2	2	2	1	4	6	2.70	1.85
Uncooperativeness	1	1	1	1	1	1	1	1	1.00	0.00	1	1	1	1	1	1	1	1	3	5	1.60	1.28
Unusual thought content	4	3	5	5	3	3	2	3	3.50	1.00	6	5	3	5	4	4	3	5	3	3	4.10	1.04
Blunted affect	4	5	4	2	5	2	5	3	3.75	1.20	4	5	6	4	3	2	4	1	4	4	3.70	1.35
Excitement	1	3	1	2	3	2	1	1	1.75	0.83	1	3	1	1	1	1	1	3	1	1	1.40	0.80
Disorientation	1	1	1	1	1	1	1	1	1.00	0.00	1	1	1	1	1	1	1	1	1	3	1.20	0.60

tive and positive symptom dimensions were calculated. This analysis was done both for the baseline and for the task condition by using Pearson correlation coefficients. In the third analysis, we evaluated the relation between regional glucose metabolism and scores for the individual symptoms of the BPRS. A Pearson correlation coefficient matrix was calculated between the BPRS variables and the relative metabolic values obtained from the baseline and the task conditions.

In consideration of the "multiple comparison problem" in the univariate tests and the multiplicity of coefficients on the Pearson's correlation analyses, we adjusted the criterion of significance to $p < .01$. We selected this criterion for statistical significance as being intermediate between the $p < .05$ value, considered significant for an individual variable, and the $p < .006$ value required by the Bonferroni adjustment; the Bonferroni criterion assumes that variables are independent (19), but the metabolic variables were highly dependent on one another. Values of $p < .05$ are reported as indicating trends.

RESULTS

Epidemiological and clinical information regarding the patients is shown in table 1. Patients classified as having predominantly negative symptoms were significantly older ($p < .05$) and were more severely ill than

the patients classified as having predominantly positive symptoms.

Table 2 shows the differences in absolute regional metabolism between the normal subjects and schizophrenic patients as a whole. The schizophrenic patients had significantly lower glucose metabolism than the normal subjects for the left and right frontal cortex during both the baseline (left frontal, $F=7.98$, $df=1,28$, $p=.008$; right frontal, $F=7.26$, $df=1,28$, $p=.01$) and the task (left frontal, $F=4.99$, $df=1,28$, $p=.03$; right frontal, $F=4.77$, $df=1,28$, $p=.04$) conditions. The ANOVA done on the relative values showed lower relative values in the frontal cortex of schizophrenic patients for the baseline (left frontal, $F=28.08$, $df=1,28$, $p=.00001$; right frontal, $F=16.9$, $df=1,28$, $p=.0003$) and for the task (left frontal, $F=18.45$, $df=1,28$, $p=.0002$; right frontal, $F=8.98$, $df=1,28$, $p=.0057$) conditions.

Classification Grouping

Table 3 gives the group means \pm SD for the absolute values of glucose metabolism for schizophrenic patients with positive or negative symptoms at baseline and during the task condition. Patients with negative symptom profiles had lower absolute metabolic values both at baseline and during the task condition than did patients with more positive symptoms. This difference between patient groups across both conditions was

TABLE 2. Absolute Regional Glucose Metabolism at Baseline and During Eye Tracking Task for Normal Control Subjects (N=12) and Patients With Chronic Schizophrenia (N=18)

Brain Region	Absolute Metabolic Value ($\mu\text{mol glucose}/100 \text{ g tissue}/\text{min}$)							
	Normal Subjects				Schizophrenic Patients			
	Baseline		Task		Baseline		Task	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Left frontal	40.34	2.95	40.20	3.82	35.23 ^a	5.53	35.74 ^b	5.89
Right frontal	39.97	2.77	39.61	3.29	35.35 ^a	5.25	35.42	5.81
Left parietal	38.61	3.58	39.42	3.48	35.33	5.30	36.41	5.70
Right parietal	38.48	2.74	39.48	2.90	35.04 ^b	4.70	35.64	5.23
Left temporal	37.33	3.10	37.79	3.69	33.97	5.33	35.04	5.41
Right temporal	37.47	2.48	37.45	2.92	34.01 ^b	4.67	34.40	4.89
Left occipital	43.20	3.95	43.96	4.16	38.75 ^b	5.20	40.52	5.84
Right occipital	44.05	4.03	44.10	3.83	39.39 ^b	5.22	40.44	5.67
Whole brain gray matter	39.67	5.11	39.76	3.47	35.87	5.21	36.49	5.47

^aSignificant differences between groups ($p < .01$).^bSignificant differences between groups ($p < .05$).**TABLE 3. Absolute Regional Glucose Metabolism at Baseline and During Eye Tracking Task for Patients With Chronic Schizophrenia Who Had Predominantly Positive (N=8) or Negative (N=10) Symptoms**

Brain Region	Absolute Metabolic Value ($\mu\text{mol glucose}/100 \text{ g tissue}/\text{min}$)							
	Patients With Positive Symptoms				Patients With Negative Symptoms			
	Baseline		Task		Baseline		Task	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Left frontal	38.25	3.84	39.59	4.05	32.85 ^a	5.50	32.67 ^b	5.30
Right frontal	38.28	3.90	39.32	3.65	33.01 ^a	5.02	32.30 ^b	5.32
Left parietal	37.78	4.21	39.84	3.80	33.37	5.28	33.67 ^a	5.48
Right parietal	37.39	4.05	38.62	3.20	33.15	4.32	33.26 ^a	5.32
Left temporal	36.47	4.40	38.23	3.92	31.97	5.17	32.49 ^a	5.07
Right temporal	36.11	4.00	37.37	2.99	32.32	4.48	32.02 ^a	4.81
Left occipital	41.51	4.33	44.56	3.39	36.54 ^a	4.76	37.29 ^b	5.37
Right occipital	41.91	4.21	43.57	2.96	37.37	5.07	37.94 ^a	6.07
Whole brain gray matter	38.51	4.45	39.92	3.66	33.75	4.79	33.75 ^a	5.11

^aSignificant difference between groups ($p < .05$).^bSignificant difference between groups ($p < .01$).

statistically significant for the values of the left frontal ($F=7.04$, $df=1,16$, $p=.02$), right frontal ($F=7.50$, $df=1,16$, $p=.02$), left parietal ($F=5.31$, $df=1,16$, $p=.04$), right parietal ($F=5.39$, $df=1,16$, $p=.04$), left temporal ($F=5.06$, $df=1,16$, $p=.04$), right temporal ($F=5.07$, $df=1,16$, $p=.04$), left occipital ($F=8.06$, $df=1,16$, $p=.02$), right occipital ($F=5.05$, $df=1,16$, $p=.04$), and whole brain gray matter ($F=6.11$, $df=1,16$, $p=.03$). In spite of the fact that the Task by Symptom Type interactions did not reach statistical significance, these differences appear to be largely due to the fact that patients with a predominance of negative symptoms failed to evidence within-subject activation in their regional metabolism during the visual task, whereas patients with positive symptoms showed a task-related increase of metabolic activity. As a consequence, the between-groups differences are clearly significant for most comparisons during the visual task condition but are not significant under the baseline condition.

Table 4 gives the group means for the relative metabolic values at baseline and during the task condition for the two groups of patients. The schizo-

phrenic patients with predominantly negative symptoms showed a trend toward lower relative frontal values (hypofrontality) that was less apparent in the other group of schizophrenic patients; however, this difference was statistically significant only for the relative metabolic activity of the right frontal cortex during the task condition ($F=5.92$, $df=1,16$, $p<.03$). Because of the more general task-related effects on absolute metabolic activity (table 3), correction for whole brain activity in the calculation of relative regional metabolic activity values (table 4) eliminates several other specific group differences that are apparent in the analysis of absolute values.

Dimensional Analyses

Table 5 gives the correlation coefficients relating the absolute metabolic values to the negative and positive symptom dimensions for the baseline and task conditions. Although statistical significance ($r=.47$, $p=.05$) was achieved between the metabolic values for the occipital cortex and the positive symptom dimension only during the baseline conditions, consistent trends

TABLE 4. Relative Regional Glucose Metabolism^a at Baseline and During Eye Tracking Task for Patients With Chronic Schizophrenia Who Had Predominantly Positive (N=8) or Negative (N=10) Symptoms

Brain Region	Regional Metabolic Value/Whole Brain Metabolic Value							
	Patients With Positive Symptoms				Patients With Negative Symptoms			
	Baseline		Task		Baseline		Task	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Left frontal	0.994	0.22	0.991	0.29	0.969	0.33	0.967	0.26
Right frontal	0.996	0.44	0.984	0.22	0.977	0.28	0.955 ^b	0.24
Left parietal	0.982	0.35	0.998	0.33	0.986	0.37	0.997	0.39
Right parietal	0.972	0.41	0.968	0.28	0.984	0.38	0.985	0.53
Left temporal	0.947	0.33	0.956	0.24	0.944	0.26	0.962	0.28
Right temporal	0.938	0.25	0.937	0.19	0.958	0.16	0.949	0.31
Left occipital	1.079	0.40	1.118	0.36	1.085	0.42	1.106	0.26
Right occipital	1.090	0.46	1.094	0.39	1.109	0.42	1.122	0.36

^aRelative values were obtained by averaging the individual relative values, not by computing the relative values based on the mean absolute values for the groups.

^bSignificant difference between groups ($p < .03$).

TABLE 5. Correlations Between Number of Positive or Negative Symptoms and Absolute Regional Glucose Metabolism at Baseline and During Eye Tracking Task for Patients With Chronic Schizophrenia (N=18)

Brain Region	Correlation Coefficient (r) ^a			
	Number of Positive Symptoms		Number of Negative Symptoms	
	Baseline	Task	Baseline	Task
Left frontal	.34		-.31	-.41
Right frontal	.31			-.40
Left parietal	.38		-.31	-.40
Right parietal	.37			-.31
Left temporal	.41		-.34	-.39
Right temporal	.40			-.35
Left occipital	.52		-.36	-.44
Right occipital	.50			-.31
Whole brain gray matter	.40		-.32	-.39

^aOnly r values above .30 or below $-.30$ ($p < .05$) are presented.

toward a positive correlation between metabolic values and the positive symptoms and toward a negative correlation between metabolic values and negative symptoms were observed. The correlation between metabolic values and the positive dimension was shown only for the baseline state, but the correlation between metabolic values with the negative dimension was greater during the task condition. The correlations between metabolic values and both the positive and the negative dimensions were higher for the cortical regions of the left hemisphere than for the contralateral right hemispheric regions.

Individual Symptom Analyses

Table 6 gives the values for the correlation coefficients relating relative metabolic values to clinical variables for baseline and task conditions. Symptoms of the BPRS with a mean rating of less than 2 for both subgroups of patients were excluded from the analyses, and only correlations above $r = .47$ or below $r = -.46$ ($p < .05$) are shown. The regional relative

metabolic activity evidenced a different pattern of correlations with the clinical variables for the baseline and task conditions. There were more significant correlations between regional metabolic activity and clinical items during the task condition—14—than there were at baseline—eight. For example, at baseline, metabolism in the frontal lobes had no significant correlation with clinical data. During the task, however, a pattern of significant *negative* correlations between metabolism in the left frontal lobe and the BPRS items of tension, depressive mood, and suspiciousness appeared. Moreover, the occipital lobes were the brain areas with the greatest number of clinical correlations in both conditions, with positive correlations to anxiety, tension, mannerisms, and suspiciousness.

DISCUSSION

Of the many attempts that have been made to classify schizophrenia, most focus on grouping phenomenological characteristics; very few attempts have depended on measures of cerebral function. This study is an attempt to investigate the relation between the *differences* in phenomenological characteristics of patients and *differences* in regional brain metabolism in response to activation by an eye tracking task. Correlations pertain to covariations between the different classes of data.

When comparing the normal subjects with the schizophrenic patients as a whole, metabolic differences were seen in the frontal lobes, which appeared hypometabolic in the schizophrenic patients both at baseline and during the task. These findings are in agreement with some of the previous studies using regional cerebral blood flow techniques (20, 21) and positron emission tomography (22–24), which have shown abnormal frontal lobe function.

The clinical distinction of the group of schizophrenic patients into those with negative and positive symp-

TABLE 6. Correlations Between Clinical Variables and Relative Regional Glucose Metabolism at Baseline and During Eye Tracking Task for Patients With Chronic Schizophrenia (N=18)

Clinical Variable	Correlation Coefficient (r) ^a													
	Left Frontal		Right Frontal		Left Parietal		Right Parietal		Right Temporal		Left Occipital		Right Occipital	
	Base-line	Task	Base-line	Task	Base-line	Task	Base-line	Task	Base-line	Task	Base-line	Task	Base-line	Task
Age		-.47												
Number of positive symptoms										.53				
Number of negative symptoms														
BPRS scores														
Somatic preoccupation				-.47										
Anxiety						.50	.48				.48	.51		
Emotional withdrawal														
Conceptual disorganization														
Tension	-.50												.51	.61
Mannerisms												.51	.53	.77
Graviosity														
Depressive mood	-.52									.53				
Hostility							.51							
Suspiciousness	-.62										.56	.61	.58	
Hallucinations									.49	.72				
Motor retardation														
Unusual thought content														
Blunted affect														

^aOnly r values above .47 or below -.46 ($p < .05$) are presented. There were no significant correlations for the left temporal region.

toms revealed the simultaneous occurrence of both positive and negative symptoms in both groups. The most chronic and severely ill patients had the highest values for measures of negative symptoms but also showed considerable florid pathology of a positive nature. When the regional metabolism was calculated separately for these subgroups of patients, the patients with predominantly negative symptoms evidenced lower regional cerebral metabolism and a lower metabolic response to the task than did the patients with predominantly positive symptoms. The association between low cerebral metabolism and chronic negative symptoms is of particular interest in view of the importance of these symptoms in the schizophrenic defect state and their association with poor outcome (25). In the comparison of the absolute metabolic values for the whole brain between the normal subjects and the two subgroups of patients, only the patients with predominantly negative symptoms had significantly lower total metabolic values than normal subjects. This association between chronicity, negative symptoms, and lower total brain metabolism may be of relevance for interpreting the 1948 report of Kety et al. (26) of failure to show lower total brain metabolism in a heterogeneous group of schizophrenic patients.

The relative metabolic activity at baseline did not reveal major differences between schizophrenic patients who were classified as having negative versus positive symptoms. However, during the visual task the patients with predominantly negative symptoms evidenced lower relative metabolic activity of the frontal regions and significantly lower activity in the right frontal lobe than did patients with predominantly positive symptoms. The symptom-related lower metabolism of the frontal cortex (hypofrontality) should be viewed in the light of previous studies that have investigated cerebral blood flow and glucose metabolism in the frontal regions of schizophrenic patients. Most of these studies reported lower metabolism and blood flow in the brains of schizophrenic patients (22-24, 27). However, other investigators have failed to replicate these findings. Widen et al. (28), using [¹¹C]-glucose and PET, found hypofrontality only in patients with chronic schizophrenia and not in those with acute schizophrenia with a predominance of positive symptoms. Similarly, Sheppard et al. (29) were unable to show hypofrontality using radioactive isotope of oxygen and PET in patients with acute schizophrenia, half of whom were not medicated. These latter studies, in conjunction with our results showing that the more

severe hypofrontality was seen in the older patients with predominantly negative symptoms, suggest that hypofrontality may be related not only to the schizophrenic process but also to aging, long-term medication, and/or an organic deficiency state.

The accentuation of hypofrontality during the task performance was greater for the right lobe and was more marked for patients with predominantly negative symptoms. Enhancement by the visual task of metabolic differences between the patients suggests the existence of cerebral functional differences between these two subgroups of patients. These differences could reflect differential capacity for cerebral activation by attentional mechanisms. Positive-symptom patients having normal or accentuated attention might show a general increase in metabolic activity response, whereas negative-symptom patients having lower attentional responses to the external environment might show minimal brain activation. However, the differences could also be related to other brain functional systems, since the visual task probably activates brain regions involved in visual memory, recognition, and association.

The effect of age versus negative symptoms on hypofrontality is unclear, since there is a clear relationship between age and the appearance of negative symptoms in schizophrenia. We attempted to disentangle the effects using analysis of covariance methods. Hypofrontality related significantly ($p < .05$) to age when negative symptoms were disregarded, and, as noted, hypofrontality was associated with the predominance of negative symptoms when age was not considered. However, neither age nor negative symptoms significantly related to hypofrontality when the effect of the other was partialled out. The relation between the affective and cognitive deterioration seen in schizophrenic patients as they grow older and the accentuation of hypofrontality and blunting of brain metabolic response to stimulation needs to be more carefully investigated (30).

The role of neuroleptics in blunting cerebral activation also needs to be excluded because patients with predominantly negative symptoms had a longer exposure to neuroleptics than the group of patients with predominantly positive symptoms.

The matrix of correlations between the clinical and the metabolic variables permitted the investigation of the association between these two factors in a dimensional way. This is relevant because the positive/negative distinction is not categorical (patients have positive and negative symptoms simultaneously). The metabolic activity displayed two markedly different patterns of association with the positive and negative symptom dimension. A positive but not significant correlation was observed between positive symptoms and absolute values of metabolic activity during the baseline state ($r = .40$). Patients having more positive symptoms tended to show higher cerebral metabolism than patients with a predominance of negative symptoms. In the former patients, the metabolic pattern at

baseline shifted on activation by the visual task, and the metabolic and clinical correlation decreased. The other trend was a negative correlation between negative symptoms and absolute metabolic values at baseline. This correlation was stronger for the metabolic value obtained during the task, suggesting that the metabolic defect associated with the predominance of negative symptoms was accentuated when the functional system processing the task was challenged. The predominant association between negative and positive symptoms with the metabolism of left hemispheric regions is in agreement with previous work suggesting a predominance of left hemispheric abnormalities in schizophrenic subjects (31).

The correlation matrix between the individual symptoms of the BPRS and regional metabolism also showed regional lateralization patterns. More specifically, the left frontal cortex showed a strong negative correlation with the BPRS symptoms of tension, depressive mood, and suspiciousness, while the right occipital cortex showed a positive correlation with the BPRS symptoms of tension and anxiety. The association between abnormalities of the left anterior regions of the brain and depression is in agreement with the reports of depressive symptoms in stroke patients with lesions in anterior regions of the left hemisphere (32).

The lateralized association between regional metabolism and anxiety, tension, and depressive mood also suggests that asymmetry patterns may be influenced by the affective state of the subjects. Left-right asymmetry patterns have been reported (33) in normal subjects with high anxiety at the time of the PET procedure.

This study shows that some phenomenological characteristics of schizophrenic patients are associated with cerebral functional derangements. More particularly, the negative symptom dimension is associated with lower cerebral metabolic values, more severe hypofrontality, and an incapacity to change the cerebral metabolic patterns in the face of external stimulation. It also provides an example of how brain metabolism as assessed by positron emission tomography combined with different cognitive tasks may be of use in further investigating functional defects of psychiatric patients.

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"Doom Anxiety" and Delirium in Lidocaine Toxicity

Stephen M. Saravay, M.D., Jane Marke, M.D.,
Maurice D. Steinberg, M.D., and Charles J. Rabiner, M.D.

Of 15 patients with psychiatric reactions to lidocaine, 12 (80%) had mood changes, 11 (73%) had "doom anxiety," eight (53%) had overt confusional states, and six (40%) had hallucinations and delusions. The authors contend that morbid fears of impending doom or the belief that death has occurred are specific manifestations of lidocaine toxicity and may be mistakenly attributed to "understandable" fears about death during the course of recovery from a myocardial infarction on the coronary care unit.

(Am J Psychiatry 1987; 144:159-163)

Lidocaine, synthesized in 1943 and first used as a local and general anesthetic, is now probably the most widely used inpatient antiarrhythmic agent (1-4) and has recently been approved for oral use. Side effects, which frequently involve the CNS, occur in 6% to 20% of patients (3, 4) but are often overlooked (5). The most common neurological side effects are dizziness, drowsiness, obtundation, coma, seizures, respiratory arrest, muscle twitching, paresthesias, dysarthria, hypacusis, hyperacusis, tinnitus, diplopia, and other visual disturbances (2).

Remarkably little has been written about the mental effects of CNS toxicity in cardiac patients despite the large number of patients at risk (6). We have been able to find only 11 published case reports of cardiac patients describing delirium, agitation, confusion, disorientation, and hallucinations (3, 6-9). In this study we describe the psychiatric manifestations of lidocaine toxicity in 15 cardiac patients and propose that "doom anxiety" (apprehension about imminent death or delusion that death has actually occurred) is a characteristic feature of the syndrome.

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METHOD

Patients with psychiatric symptoms who were treated with lidocaine were referred during weekly cardiac care unit liaison rounds with the nursing staff and from consultation-liaison psychiatry residents alerted to our research interests. Only those subjects who could be interviewed were accepted into the study. Each chart was thoroughly reviewed. Recorded data for each 8-hour shift included notations about mental symptoms and emotional condition; the time, dose, and rate of administration of lidocaine; and time and dose of other antiarrhythmic agents and any other potentially psychotoxic drugs such as morphine sulfate, hydromorphone hydrochloride, and digitalis. Any physical condition capable of inducing acute brain syndromes or abnormal laboratory values consistent with such syndromes were also noted. We wished to rule out the possibility that a hypotensive episode, which can be an unusual complication of rapid administration of lidocaine in states of impaired circulation (10, 11), might be responsible for the psychiatric symptoms in our patients; we therefore recorded the patients' lowest systolic and diastolic blood pressure readings for each shift. Age and weight, also risk factors for lidocaine toxicity (3), were recorded as well. Congestive heart failure, poor cardiac output, and liver failure were also noted, since these conditions are known to alter the pharmacokinetics of lidocaine.

A diagnosis of a psychiatric reaction to lidocaine was made if the psychiatric signs and symptoms were clearly related to time and/or rate of lidocaine administration and could not reasonably be attributed to other medications or intercurrent disease.

RESULTS

Of 32 patients screened, 15 met the criteria. For three of the 17 excluded patients, there was no correlation between symptoms and lidocaine. In 12, concurrent events such as acute congestive heart failure, hyperthyroidism, electrolyte disorder, administration of other antiarrhythmics or morphine sulfate, or toxic levels of digitalis prevented the attribution of psychiatric symptoms to any single cause.

Primary diagnoses in our subjects were myocardial

infarction (N=8), arrhythmia (N=4), and congestive heart failure (N=3). Three patients (20%) died during hospitalization, none due to lidocaine toxicity; this rate is comparable to that of the Boston Collaborative Study (3). Although some patients had hypotensive readings (table 1), none of the hypotensive periods were synchronous with the appearance of psychiatric reactions to lidocaine. Table 1 summarizes the study population and the manifestations of lidocaine toxicity.

In 12 cases (80%), neurological signs and symptoms of lidocaine toxicity accompanied the mental symptoms. The rates of administration were consistent with the appearance of toxicity. Rates above 50–55 $\mu\text{g/kg/min}$ are likely to cause toxicity (12–14), while rates between 40 and 45 $\mu\text{g/kg/min}$ produce toxicity in 15% of patients (15). Rates above 30 $\mu\text{g/kg/min}$ may be toxic in patients with advanced heart failure (1), which, like cardiogenic shock, may increase blood levels three- to tenfold (2) and elevate levels of lidocaine's active metabolites (16). As little as 50 mg of lidocaine given as an intravenous bolus can cause CNS toxicity even in the absence of failure or shock (17). In 11 patients lidocaine was administered at a rate greater than 50 $\mu\text{g/kg/min}$. Of the other four, three had congestive heart failure; one of these also had cardiogenic shock. The remaining patient (patient 7) had the mildest clinical reaction of the entire sample. He was frightened by the sensation of a bomb going off in his head.

Twelve patients (80%) had mood changes of anxiety and/or depression, while one anxious patient also became hostile. Eleven (73%) had doom anxiety. Eight patients (53%) had clinical manifestations of an acute brain syndrome as manifested by overt confusion or disorientation. Six (40%) had hallucinations and delusions; these patients also had overt acute brain syndromes. One patient had an anxiety reaction, and another became anxious about a disturbing sensation, as if a bomb were going off in his head, during an injection of a bolus of lidocaine. One other patient also described this phenomenon, along with other symptoms. In no case were hypotensive episodes temporally related to the appearance of doom anxiety.

Four patients (27%) had the persisting anxiety-laden conviction that they had been on the brink of death. Three patients, who subsequently broke down and wept when reviewing their experiences, had the most severe acute brain syndromes, with hallucinations and delusions.

DOOM ANXIETY

Doom anxiety in this paper refers to the apprehensiveness associated with death-related content and differs from the phobic fear of death commonly seen in panic attacks in that it carries with it a greater sense of conviction, at times reaching delusional proportions. A lugubrious emotional tone often persists for hours or

TABLE 1. Characteristics of 15 Patients With Psychiatric Reactions to Lidocaine

Patient	Age (years)	Sex	Weight (lb.)	Toxicity Risk Factors	
				Systolic Blood Pressure <100 mm Hg	Congestive Heart Failure
1	68	F	104	Yes	
2	49	M	173		
3	56	M	255		Yes
4	81	F	124		Yes
5	79	M	135	Yes	Yes
6	61	M	200		Yes
7	59	M	155		
8	52	M	178		Yes
9	50	M	175		
10	79	M	115		Yes
11	70	M	130		
12	70	M	168		
13	70	M	200		
14	66	M	170		
15	66	M	125		

days afterward and is accompanied by preoccupations and ruminations of morbid content about wills, life insurance, autopsies, departing the world, and so forth, not seen in typical panic attacks in our clinical experience. Doom anxiety was not associated with hypotensive episodes, was not more frequent in patients who later died, and did not appear to be related to the seriousness of the cardiac disease.

Case 1 (patient 3). Five minutes after a lidocaine drip was begun at a rate of 33 $\mu\text{g/kg/min}$, this 56-year-old man noticed that his ears had become clogged, and his voice sounded funny to him. These sensations disappeared within 10 to 15 minutes, and the lidocaine drip was continued for several hours. During this time he became agitated and irritable and had a jumpy feeling that prevented him from lying down or staying still; "everything was bothering me." He remembered wondering "Will I ever get out of here?" He felt short of breath and experienced air hunger in the absence of any objective physical cause and believed that his death was imminent. He recalled having had morbid thoughts because he had not made out a will and had not signed over to his wife a check that had recently come in. His morbid ruminations and fear of dying remitted completely within one-half hour of the discontinuation of the lidocaine drip.

Case 2 (patient 9). Within the first 2 days of his admission and during a lidocaine drip at a rate of 56–60 $\mu\text{g/kg/min}$, this 50-year-old man experienced bells ringing all over and getting louder and louder. Frightened, he reached for the bell near his bed and pressed it, only to have the illusion that the stem was missing and that no one was able to recognize or respond to his distress. He broke down and cried; the nurses came and explained to him that he was probably having a reaction to his medication which would pass in a few minutes, and it did. When interviewed several days later, he was still depressed and convinced that he would die. He related his conviction to the toxic reaction to lidocaine, concluding at that time that these symptoms during his second heart attack heralded an inexorable downhill course. The patient, an electrical engineer, believed an electrical feedback system had been established in his heart that would

Lidocaine Administration Rate ($\mu\text{g/kg/min}$)	Psychiatric Reactions					
	Death Fears	Acute Brain Syndrome	Perceptual Disturbances	Delusions	Mood Changes	Wept at Interview
51		Yes		Persecutory		Yes
51		Yes	Visual hallucinations	Grandiose	Anxious	
33	Yes				Anxious	
47	Yes	Yes			Anxious	
64	Yes		Visual illusions		Depressed	
31	Yes	Yes	Visual illusions		Anxious	
47						
54	Yes	Yes			Anxious	
56	Yes		Auditory and visual illusions		Depressed	
72	Yes					
322		Yes	Auditory hallucinations	Persecutory	Anxious, hostile	Yes
61	Yes				Anxious, depressed	
62	Yes	Yes		Persecutory	Anxious, depressed	
52	Yes				Anxious	
78	Yes	Yes	Visual hallucinations		Anxious, depressed	Yes

inexorably destroy it. After several sessions of supportive psychotherapy, he felt very relieved. Several months later, when he was rehospitalized for cardiac catheterization due to recurrent angina, he was cheerful and optimistic.

Case 3 (patient 14). This 66-year-old man felt a wave of weakness proceed from his head and shoulders down to the rest of his body and felt numbness all over his body and slight nausea that began during a bolus and subsequent intravenous drip of lidocaine. He became alarmed and called the nurse. He felt his arm going numb, felt paralyzed, and felt he could hardly talk. His vision became blurred, and his head felt as though it was going to explode. He retched, became very weak, and could barely raise his arms.

When asked if he thought that he might have been on the verge of death, he recalled that he had wondered "maybe they should call my wife to come before I go. I thought I was going to die."

Lidocaine Reactions and Resuscitation After Cardiac Arrest

Two of the patients who were resuscitated after cardiac arrest, while they were not receiving lidocaine, did not describe the doom anxiety that they had experienced during prior lidocaine reactions.

Case 4 (patient 5). During his lidocaine reaction this 79-year-old man said, "That was worse than an autopsy. I am going. Goodbye." He underwent a personality change for several days, from a feisty raconteur to a despondent and resigned man preoccupied with death. No such change had occurred when he was resuscitated after an actual cardiac arrest.

Case 5 (patient 6). During his lidocaine reaction, this 61-year-old man hallucinated silver foil-like material and bell-shaped objects and felt that he was sinking or being dragged under, dragged down. He became confused and frightened that he was dying. When he was questioned after a subsequent cardiac arrest and defibrillation, he denied

experiencing the sinking feeling or morbid fears about death that he had had during the lidocaine reaction.

Lidocaine Procainamide Toxicity

Three patients in our study had separate reactions to lidocaine and procainamide. All three had doom anxieties with their reaction to lidocaine, while two of the three with a procainamide reaction also had death-related fears. In both of the last two patients, the doom anxiety arose in a florid, hallucinatory, delirious reaction with paranoid delusions.

Case 6 (patient 4). As her lidocaine was being titrated up, this 81-year-old patient voiced fears that she was afraid she was going to die. The patient later recalled, "I couldn't grasp anything; if only I could feel something. When I felt Jim's [her son-in-law's] hand I knew I was alive . . . I felt I was dying . . . I was on the road to God or something."

By contrast, several days later, when she was receiving only procainamide, 1000 ml/day, she became agitated and confused, wept, and became violent, requiring two male aides to hold her down. Retrospectively, she described a vivid hallucinatory delirium in which she believed she was variously at the governor's home talking with his family and pursued by drug addicts who were after her money. She also felt she was dead. "I thought I was dead. They were trying to get my son-in-law's money, and I thought they had already killed me. Everything was so clear," she said. Her mental state cleared within 24 hours after the discontinuation of procainamide.

Case 7 (patient 8). After boluses and a lidocaine drip shortly after admission, this 52-year-old man became very anxious, asked for his wife, and expressed thoughts of dying. This reaction cleared with the discontinuation of lidocaine. Subsequently, while the patient was receiving procainamide, he was found to have toxic blood levels of 11.7 and 13.6 $\mu\text{g/ml}$; during this time he was depressed and felt that the staff were trying to do away with him and were using needles and injecting tubes with materials to kill him. He heard some

talking coming from "upstairs" through the ceiling and some talking about people doing away with him. He was very guarded and suspicious when getting into this area; his affect was labile, and he broke down in tears when the issue of his fears about his progress was discussed. His condition improved with the reduction of his procainamide levels.

Patients' Explanations of Doom Anxiety

Although it was not done systematically, we asked some of the patients later in the study why they felt they had feelings of doom. Four patients offered explanations. One related it to a sensation of sinking, one to the inability to grasp or feel things properly. Two other patients did not relate their doom anxiety to such feelings of estrangement or detachment from reality, although one of the two did have such an experience.

DISCUSSION

Because of the nature of the study design, we cannot provide figures on the prevalence of doom anxiety. While it would have been preferable to have blood levels of lidocaine and its metabolites, we were unable to obtain them. Since the study was not blind, a selection bias may have increased the representation of patients with doom anxiety in our sample.

Any untoward experience on a coronary care unit might cause one to fear that death was near. Such concerns might contribute to the content of hallucinations or delusions that might occur during an acute brain syndrome. In the absence of a blind and controlled study, the proposed association between doom anxiety and lidocaine toxicity in our data must be considered tentative.

With this caveat in mind, our results suggest more than a coincidental relationship. The appearance of doom anxiety in our patients was restricted to the period of lidocaine administration, was concurrent with other neurologic signs and symptoms of lidocaine toxicity in over 80% of the patients, and occurred without any concurrent medical event or drug administration likely to affect the CNS. The actual risk of death due to CNS toxicity in our patients was small (3), and there was no correlation between doom anxiety and actual mortality. Of the two patients who had had doom anxieties during a lidocaine reaction, neither reported any anxieties about dying before or after they were resuscitated following cardiac arrest. Indeed, the syncope from ventricular arrhythmias and cardiac arrest usually induces euphoria and calm, probably due to the release of endorphins (18).

The literature provides further support for doom anxiety as a feature of lidocaine toxicity. It has been described in noncardiac patients with conditions that are not life threatening. In one case, a physician experienced a vivid fear of impending doom after 700 mg of lidocaine were given as a local anesthetic (19). In another, a 34-year-old woman had a sense of impending

ing doom and repeatedly announced that she was going to die after a pudendal block of 500 mg of lidocaine without epinephrine (20).

Two of our three cases of toxic reactions to procainamide, a close congener of lidocaine, had death-related content not previously described in the sparse literature on the subject (21, 22). Procaine, which provokes CNS toxic reactions virtually identical to those of lidocaine, can cause doom anxiety and dysphoric reactions when it is given intravenously as a general anesthetic (23) or administered in penicillin G procaine. At least 36 patients have been described who, as a result of the administration of penicillin G procaine, have experienced intense terror of imminent death or the conviction of having died, along with apprehension, hallucinations, and agitation, with recurrent symptoms in some for up to several months (24-28). Toxic levels of procaine may occur with routine injections of penicillin G procaine (28, 29), and inadvertent intravenous injection may be responsible (24, 28).

Three of our patients (30) with the most severe acute brain syndromes had delayed emotional reactions during the interview, and the opportunity to integrate their experiences after the fact seemed to be important to them.

It is curious that despite many descriptions of morbid doom anxiety attributed to lidocaine and procaine in noncardiac patients in clinically benign situations, few reports could be found about cardiac patients despite the enormous number of patients treated with these antiarrhythmic agents on cardiac care units. We have frequently seen astute clinicians, psychiatric and medical, uncritically ascribe doom anxiety and the associated anxiety and depression to an unexpected turn in the course of the disease. It is hoped that the findings reported in this study will encourage physicians to more carefully consider lidocaine toxicity as a possible cause of these symptoms and spur further research into the CNS toxicity of lidocaine and related antiarrhythmics.

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Psychiatrist-Patient Sexual Contact: Results of a National Survey, II: Psychiatrists' Attitudes

Judith Lewis Herman, M.D., Nanette Gartrell, M.D., Silvia Olarte, M.D.,
Michael Feldstein, Ph.D., and Russell Localio, J.D., M.P.H., M.S.

In a national random-sample survey of 1,423 practicing psychiatrists, the overwhelming majority of the respondents (98%) said that therapist-patient sexual contact is always inappropriate and usually harmful to the patient. However, 29.6% said that such contact after termination of therapy might sometimes be acceptable. Psychiatrists who acknowledged having had sexual contact with one or more patients (N=84) differed markedly from their peers in their attitudes. The majority (74%) of these offenders believed that sexual contact could be appropriate after termination; many apparently rationalized their behavior in this manner. The authors discuss the need for systematic professional education on the subject.

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The Hippocratic oath (1) and the American Psychiatric Association (APA) code of ethics (2) explicitly prohibit sexual contact between psychiatrist and patient. Nevertheless, some psychiatrists do become sexually involved with their patients. Although documentation of the extent of the problem is limited, the best available data indicate that 6%-10% of psychiatrists have had sexual contact with their patients (3, 4) and that the majority of psychiatrists have knowledge of such cases but do not intervene (5, 6). Although the numbers of malpractice claims (7) and complaints before ethics committees and licensing boards (8) have increased in recent years, it is generally agreed that only a very small fraction of these cases ever come to public attention.

In an effort to develop a more realistic estimate of

the scope of this problem, we undertook a national survey of practicing psychiatrists. An attempt was made both to document the prevalence of sexual misconduct and to understand the range of psychiatrists' attitudes and beliefs on this subject. We predicted that significant gender differences would be found both in attitudes and in practices and that psychiatrists who become sexually involved with patients would differ from their peers in attitudes as well as in behavior. Further, we speculated that it might be possible to identify a set of attitudes associated with high risk for sexual misconduct. Here, we report the results of our findings on psychiatrists' attitudes.

METHOD

A 34-item questionnaire was sent to 5,574 psychiatrists randomly selected from the American Medical Association (AMA) Masterfile. Details of the study design can be found in a previous report (3). A major portion of the questionnaire sought to probe psychiatrists' attitudes toward sexual contact between patient and therapist. Respondents were asked for their personal opinions about whether therapist-patient sexual contact might be appropriate in some circumstances. These opinions were solicited for a range of sexual behaviors (from hugging to genital contact), a range of possible indications (for example, to enhance the patient's self-esteem), and a range of settings (during treatment sessions, concurrent with therapy but outside of scheduled sessions, or after termination). In addition, respondents were given an opportunity to describe any other circumstance in which they considered sexual contact with a patient appropriate.

We also asked respondents about their beliefs regarding the effect on the patient of sexual contact with a therapist. This multiple-choice question offered the following options: usually beneficial, sometimes beneficial and sometimes harmful, no effect, usually harmful, or other (specify). Finally, respondents were asked several questions about their knowledge of APA's position on this matter and their recommendations regarding APA policy. Forced-choice items asked respondents to agree or disagree that APA should "not concern itself with this issue," "hold education semi-

Received Jan. 21, 1986; revised June 11, 1986; accepted Aug. 6, 1986. From the Departments of Psychiatry of Harvard Medical School at the Cambridge Hospital, Cambridge, Mass., Beth Israel Hospital, Boston, and New York Medical College, Valhalla, N.Y.; the Department of Biostatistics at the Harvard School of Public Health; and the Risk Management Foundation of the Harvard Medical Institutions. Address reprint requests to Dr. Herman, 61 Roseland St., Somerville, MA 02143.

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nars and/or discussion groups on this topic," "make recommendations for professional assistance to therapists and patients involved in such activity," and "take disciplinary action against the therapists involved in such activity."

The anonymous responses were key punched and tabulated. Data analysis was conducted by means of chi-square computation (without continuity correction). We used Fisher's exact test in all cases for which expected cell frequencies were too small for accurate use of chi-square as a test of significance.

RESULTS

Majority Views

Completed questionnaires were returned by 1,423 psychiatrists (26%). The respondent group was nearly identical in gender distribution to that of the AMA Masterfile for psychiatry. Respondents were slightly younger and more likely to be Board certified than the survey group as a whole. Eighty-seven percent of the respondents had completed an accredited psychiatric residency, 84% were APA members, and 67% had undergone personal psychotherapy or psychoanalysis. Fifty-seven percent were Board certified. The characteristics of the respondents are described more fully in our previous report (3).

By an overwhelming majority (98%), the respondents believed that sexual contact between patient and therapist is always inappropriate during therapy sessions or concurrent with treatment. Moreover, the great majority (97.4%) believed that such contact is usually or always harmful to the patient. Although "always harmful" was not offered as a forced-choice option on this question, it was written in by 13% of the respondents. Many commented spontaneously that they considered such behavior equivalent to rape.

The majority of the respondents (68%, 960 of 1,408 who answered the question) said that hugging a patient could be appropriate in some circumstances but drew the line at this form of contact. Only a small minority (11%, 160 of 1,406) thought that kissing could ever be an appropriate contact, and less than 5% believed that fondling, sitting on a lap, disrobing, or genital contact is appropriate under any circumstances.

The great majority of the respondents also rejected all of the proposed indications for sexual contact with a patient. Less than 2% believed that such contact could be appropriate for enhancement of the patient's self-esteem, as a corrective emotional experience for the patient, to shorten a grief reaction, or to convert a patient from one sexual orientation to another. Four and one-half percent thought such contact might be indicated for treatment of sexual dysfunction; many of these respondents specified the use of surrogates in sex therapy. Four and one-half percent thought sexual contact could be appropriate in the event that the

therapist fell in love with the patient, and an additional 4% reserved judgment in this instance. Written comments from a number of respondents indicated that they were disposed to allow exceptions to the code of professional ethics in the name of romantic love. As one respondent, a 34-year-old married man, wrote, "If you fall in love, end the therapy. At that point there are no rules."

The belief that the prohibition against sexual contact with a patient ends with the termination of therapy was shared by a considerable minority of the respondents. Four hundred six of 1,370 (29.6%) who answered the question said that such contact could sometimes be appropriate after termination, and an additional 8.5% (116 of 1,370) had no opinion on this question. Moreover, 17.4% (241 of 1,383) thought that the APA position permits sexual contact after termination of therapy. The many written comments indicated a wide range of opinions and considerable confusion on the matter of sexual relationships after termination. A few respondents stated explicitly that the prohibition against sexual contact with a patient had no time limit and could not be abrogated by termination. A 32-year-old divorced man wrote, "Once someone walks through the door as a patient, they can *never* be a friend or lover, etc. This still leaves me about 5 billion other people to be involved with." A larger number appeared reluctant to close off this option absolutely. A 41-year-old married man, in practice for 12 years, described his personal guidelines as follows: "I believe that under certain circumstances sexual contact with former patients could be regarded as permissible. I have seen more than one highly successful marriage develop in this way. I favor a minimum of 6 months posttermination for beginning any sexual activity. There should be a 6-24-month gray zone. After 2 years, no restrictions." Others proposed time limits ranging from 1 year to decades.

A number of respondents proposed professional consultation as a method of distinguishing permissible from impermissible relationships. A 50-year-old married man, in practice for 21 years, offered this guideline: "If love between patient and doctor is genuine and not a transference-countertransference phenomenon, and if the patient is referred to another therapist to help in that determination, then genital contact between the *now former* patient and doctor *may be* appropriate."

Many respondents also indicated a belief that, while casual sexual contacts with a patient could not be condoned even after termination, such contacts could be countenanced if both patient and therapist were seeking marriage or a serious love relationship. For example, a 55-year-old married man wrote, "After termination of therapy, if both the patient and therapist fall in pure love and both are single, no one can bother their sexual contact."

The great majority of the respondents (96%) thought that APA should concern itself with this issue. Ninety-two percent said that professional assistance

TABLE 1. Offenders' and Nonoffenders' Responses to Survey on Psychiatrists' Attitudes About Sexual Contact With Patients

Factors That Can Make Sexual Contact Always or Sometimes Appropriate ^a	Offenders			Nonoffenders			p (Fisher's exact test)
	Total N	Agree N	%	Total N	Agree N	%	
Setting							
After termination	81	60	74.1	1,192	326	27.4	.0001
During treatment sessions	84	8	9.5	1,201	17	1.4	.001
Concurrent with treatment	83	7	8.4	1,203	7	0.6	.001
Activity							
Hugging	84	77	91.7	1,224	817	66.7	.00001
Kissing	84	26	31.0	1,222	131	10.7	.00001
Sitting on lap	84	14	16.7	1,224	38	3.1	.0001
Disrobing	84	8	9.5	1,224	19	1.6	.001
Fondling	84	5	6.0	1,225	6	0.5	.0001
Genital contact	84	5	6.0	1,226	5	0.4	.0001
Indication							
Therapist in love with patient	84	18	21.4	1,224	43	3.5	.0001
Sexual dysfunction	84	15	17.9	1,224	48	3.9	.0001
Enhance self-esteem	84	9	10.7	1,228	11	0.9	.0001
Corrective emotional experience	83	7	8.4	1,225	6	0.5	.0001
Change sexual orientation	84	6	7.1	1,227	9	0.7	.001
Shorten grief reaction	84	5	6.0	1,226	10	0.8	.01

^aThese results reflect responses to forced-choice questions. The four possible responses were 1) always appropriate (chosen by less than 3% of the respondents in all cases), 2) sometimes appropriate, 3) always inappropriate, and 4) no opinion. Percentages in this table represent the sum of responses 1 and 2. The p values are for 4×2 tables. Total N varies slightly because not all respondents answered all questions.

should be offered to patients and therapists who become involved in sexual relationships. Eighty-nine percent thought that educational seminars or discussion groups on this topic should be held, and 86% thought that APA should take disciplinary action against offending therapists. The only significant gender differences in attitudes appeared on these policy questions, with a larger proportion of women than men favoring an activist stance. Women were somewhat more likely than men to favor APA involvement ($\chi^2=5.84$, $df=1$, $p<.05$), educational programs ($\chi^2=10.42$, $df=1$, $p<.01$), treatment for involved therapists and patients ($\chi^2=8.06$, $df=1$, $p<.01$), and disciplinary measures against offending therapists ($\chi^2=6.7$, $df=1$, $p<.01$).

Attitudes of Offenders

Psychiatrists who acknowledged having had sexual contact with one or more patients ($N=84$, or 6.4% of the 1,316 respondents to this question) differed markedly from their peers in their attitudes. The majority of the offenders said that sexual contact is inappropriate in most circumstances; however, they were much more apt to allow for exceptions to the general rule. The exception most commonly granted was for sexual relations after termination of therapy. Seventy-four percent of the offenders believed that sexual relations could be appropriate after termination; 27.4% of the nonoffenders thought so (see table 1). Since most of the offenders also reported that their sexual relations with their patients began shortly after termination, it appeared that their behavior was congruent with their belief that such relations were permissible. The offenders also tended to allow greater latitude than their

peers in the name of romance. Twenty-one percent of the offenders believed that sexual contact could be appropriate if the therapist fell in love with the patient, as opposed to 3.5% of the nonoffenders (Fisher's exact test, $p<.0001$).

A considerable minority of the offenders also countenanced sexual relations with patients in the guise of therapy. Nineteen percent of them said that sexual contact could sometimes be beneficial to patients, compared with 1% of the nonoffenders ($\chi^2=118.22$, $df=3$, $p<.0001$). Nearly 10% of the offenders thought that sexual relations could sometimes be appropriate as a therapeutic intervention during treatment sessions, whereas only 1% of the nonoffenders thought so. The offenders were significantly more likely than the nonoffenders to recognize sexual contact as a therapeutic modality for treating sexual dysfunction, enhancing the patient's self-esteem, providing a corrective emotional experience for the patient, converting a patient's sexual orientation, or shortening a patient's grief reaction after a significant loss. The offenders also differed from the nonoffenders in the range of physical contacts between therapists and patients that they considered permissible within the context of treatment (see table 1).

Within the offender group, no significant attitudinal differences were observed between those who acknowledged sexual activity with patients only after termination and those who acknowledged sexual activity during or concurrent with treatment. However, offenders who admitted to sexual contact with more than one patient emerged as a distinct subgroup. Repeat offenders were particularly likely to believe in the therapeutic value of sexual relations with patients. Ten of the 16 offenders who considered such relations

potentially beneficial to patients were repeaters (Fisher's exact test, $p < .02$). The majority of the offenders who condoned sexual relations within the treatment setting or concurrent with treatment—and who accepted such therapeutic indications as enhancing a patient's self-esteem, providing a corrective emotional experience, or changing a patient's sexual orientation—were also repeaters.

An example of sexual contact rationalized as a therapeutic intervention was described by a 57-year-old married woman who had maintained a sexual relationship with a schizophrenic male patient concurrent with his treatment. The intent of this relationship was "extension of reparenting from infantile stage to adult over a period of years." This psychiatrist was pleased to have had the sexual contact and thought it was beneficial to her patient but stopped because it was "too much trouble—I'm an open person and the secretiveness was not to my liking." She had consulted with her former analyst who had apparently supported this treatment plan.

Although most offenders did not think that the sexual relationships in which they engaged were therapeutic for their patients, they believed that these relationships were at best mutually satisfying and at worst innocuous. A 55-year-old divorced man, in practice for 24 years, who acknowledged sexual contact with three female patients, wrote of his most recent relationship that it was "a loving relation to a healthy human being I'd come to know." He added that this relationship "in *no way* had the usual sordid tinge." Others, less enthusiastic about their experiences, still tended to minimize the possibility of harm. A 44-year-old single man who had had sexual relations with two male former patients wrote, "I learned from this experience—no harm was done that I can see—and now, for me personally, former patients are off my list."

Even those who believed that such contacts are usually harmful to patients and who regretted their own experiences had great difficulty recognizing that they had injured their patients. Only eight (9.5%) believed that their patients experienced the sexual relationship as harmful. Only one offender expressed regret based on an empathic appreciation of the meaning of the sexual contact to the patient. This was a 31-year-old man who became involved with a patient during his psychiatry clerkship as a medical student. He saw the involvement as having "no therapeutic intent, simply a loss of impulse control on my part, not in love but in lust" and afterward felt great remorse: "I saw her disappointment in me, her own guilt/shame for 'breaking' me, possibly an increased realization on her part of her craziness." He added that he did not seek consultation because he was too ashamed of what he had done.

With few exceptions, those who regretted the sexual contact tended to focus on the adverse consequences that they themselves had suffered, rather than the harm done to their patients. A 30-year-old married man who

had become sexually involved with a patient during residency wrote that he had been devastated by the experience: "I find it hard to believe I did what I did. It cost me my self-esteem, nearly cost me my marriage, and may yet cost me my job or career." He was less certain, however, about the effect of the sexual relationship on his patient, a frequently and severely abused incest victim: "It is difficult for me to say how harmful the episode was to my patient. Her life was terribly chaotic to begin with, with multiple moves, suicide attempts, substance abuse, etc."

Finally, the offenders differed significantly from their peers in their policy recommendations regarding this issue. Not surprisingly, they were much more likely than nonoffenders to oppose any form of disciplinary action (34%, 26 of 77, versus 13%, 156 of 1,175; $\chi^2 = 24.42$, $df = 1$, $p < .0001$). Repeat offenders were the most likely to find the idea of disciplinary action objectionable (46%, 12 of 26), but the difference from one-time offenders did not reach statistical significance (Fisher's exact test, two-tailed, $p = .08$; the inferences remain unchanged after a Bonferroni adjustment for multiple comparisons on this variable).

Some offenders protested what they considered an exaggerated concern for the welfare of patients. For example, a 49-year-old married man, in practice for 20 years, wrote, "A large number of patients are very capable of managing their affairs and should not be treated as children who need protection." This psychiatrist acknowledged sexual relations with two female patients. Of his most recent relationship he wrote simply, "It has been fun." Others objected to current sanctions against sexual contact with patients on behalf of the patients themselves. A 48-year-old married man, in practice for 18 years, said that sexual contacts with patients are "mostly harmful but in special instances could become lifesaving." This psychiatrist acknowledged sexual contact with seven female patients. His policy recommendations were as follows: "Until APA decides to become more lax, the involvement is quite taxing on the therapist and the pleasure is not worth the stress and anxieties (professional suicide). APA should loosen up and become more understanding."

DISCUSSION

This survey demonstrates that most psychiatrists endorse an absolute prohibition against sexual contact with patients. By large majorities, the respondents in the survey affirmed their belief that such contacts are always inappropriate and usually harmful to patients. However, considerable confusion was apparent regarding the issue of sexual relations after termination of therapy. A sizable minority of the respondents thought that the APA code of ethics permits such contacts, and a somewhat larger number considered such contacts permissible according to their own personal ethical code. Of greatest concern is the finding

that 74% of the acknowledged offenders believe that such contacts are permissible and apparently invoke this belief to rationalize their own behavior.

Although the APA *Principles of Medical Ethics* states that sexual activity with a patient is unethical, the matter of sexual contact after termination of therapy is not explicitly addressed. A 1983 casebook of APA Ethics Committee opinions (9) raises this question but fails to offer an unequivocal answer. A thorough search of the literature yielded very few references in which this matter was discussed. Greenacre (10), in a 1954 paper on the role of transference, indicated her belief that the prohibition against sexual contact with patients applies as well to relationships established "relatively soon after" termination. This statement may imply a belief that such relationships are permissible after a delay of unspecified duration. In two influential articles written in the 1970s, Perr (11) and Marmor (12) argued that exceptions to the ban on sexual contact may be allowed if the therapist falls in love with and/or wishes to marry the patient, provided that the therapist terminates the professional relationship and refers the patient elsewhere for treatment. Marmor, however, qualified his argument as follows:

I must still affirm my clinical conviction that the therapist to whom this happens has failed in his primary responsibility to the woman who came to him as a patient. I make this statement in full knowledge of the fact that a number of prominent psychiatrists and psychoanalysts have married former patients. How many others who did not reach this honorable end-point, have nevertheless rationalized their loss of self-control on the basis of "falling in love" with their patients I do not know. My point, however, is that such a rationalization should not obscure the fact that whenever this happens, the psychotherapist has not been able to master his countertransference feelings. (12, p. 7)

More recently, a few authors have taken the position that the prohibition against sexual contact between patient and therapist is permanently established with the initial encounter and cannot be abrogated by termination. Anderson, in an unpublished paper (Ethics Committee, Massachusetts Psychiatric Society, 1978), argued that the therapist enters into an "ethical covenant" with his patient which "changes the obligations for all time." Relationships established after termination may be friendly, but they are not egalitarian, because the therapist must remain available so that the patient can reenter therapy at some future time if the need arises: "The ex-therapist must still always put the needs of his ex-patient first, in order not to abandon or exploit his patient." A.N. Brodsky, in a paper presented at the 1983 annual meeting of the American Psychological Association, argued further, "Father-daughter incest does not become acceptable one year after the daughter has left home. No matter how the therapy contract ends, the imbalance of power of the initial interactions can never be erased."

Numerous other authors have compared the prohibition against sexual contact with patients to the incest taboo (13-17). This analogy accurately describes both the psychodynamics and the reality of the power relationship. Patients enter therapy in need of help and care. By virtue of this fact, they voluntarily submit themselves to an unequal relationship in which their therapists have superior knowledge and power. Transference feelings related to the universal childhood experience of dependence on a parent are inevitably aroused. These feelings further exaggerate the power imbalance in the therapeutic relationship and render all patients vulnerable to exploitation. The promise to abstain from abusing this position of power for personal gratification is central to the therapeutic contract; violations of this promise destroy the basic trust on which the therapeutic process is founded.

Neither transference nor the real inequality in the power relationship ends with the termination of therapy. In our opinion, the notion that exceptions to the rule of abstinence can be allowed in the name of love or marriage reveals either a naive romanticism or an insufficient understanding of the nature of the therapeutic relationship or both. Similarly, pragmatic efforts to define a posttermination waiting period, after which sexual relations might be permissible, disregard both the continued inequality of the roles of the therapist and former patient and the timelessness of unconscious processes, including transference.

Historically, a minority of psychiatrists and other mental health professionals have advocated sexual contact with patients as a therapeutic modality (18, 19). Such beliefs have always been considered unorthodox and have generated great controversy. However, some prominent psychiatrists continue to espouse the view that sexualized therapy may at times be beneficial to patients. For example, with the publication of papers of Sabina Spielrein (20), it became known that Jung had seduced one of his first psychoanalytic patients. Bettelheim, in an essay prompted by these revelations (21), described Jung's conduct toward his patient as "callous" and "inexcusable." However, he then credited Jung for the patient's recovery from an episode of serious disturbance in adolescence: "However questionable Jung's behavior was from a moral point of view—however, unorthodox, even disreputable, it may have been—somehow it met the prime obligation of the therapist toward his patient: to cure her. True, Spielrein paid a very high price in unhappiness, confusion, and disillusion for the particular way in which she got cured, but then this is often true for mental patients who are as sick as she was."

The results of our survey indicate, however, that the overwhelming majority of psychiatrists reject the idea that sexual contact with a therapist can ever be beneficial or therapeutic for patients. The belief in the therapeutic efficacy of sexual contact appears to be largely confined to repeat offenders.

It is encouraging to note that even in the absence of

specific education on this subject, the majority of psychiatrists appear to understand and affirm the absolute prohibition against sexual contact with patients. However, in the absence of a clear and explicitly defined national APA policy, a considerable minority of psychiatrists currently believe that this prohibition ends with the termination of the therapy relationship or that it can be waived for love or marriage. This belief is particularly common among offenders, who apparently most often rationalize their behavior in this manner. Furthermore, offenders appear particularly unable to recognize the harmfulness of their behavior, and a number of them espouse an "underground" belief in the therapeutic benefits of sexual contact with patients. These findings indicate a need for systematic education of psychiatrists on this issue. We recommend that APA amend its *Principles of Medical Ethics* to include a statement explaining the nature of the harm done to patients by sexual contact and explicitly affirming that such contact is unethical whether it occurs before or after termination. Further, we believe that APA should undertake leadership responsibility for developing specific educational programs on this subject and requiring that such education be included as a criterion for completion of accredited specialty training and Board certification.

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Multiple Hormonal Responses to Insulin-Induced Hypoglycemia in Depressed Patients and Normal Volunteers

Jay D. Amsterdam, M.D., Edward Schweizer, M.D., and Andrew Winokur, M.D., Ph.D.

Studies have shown that some depressed patients may demonstrate multiple hormonal response abnormalities after a neuroendocrine challenge test; this finding has suggested the strategy of measuring several hormones after an insulin tolerance test. The authors gave insulin tolerance tests to 72 depressed patients and 51 age- and sex-matched healthy volunteer control subjects and measured glucose, cortisol, prolactin, and human growth hormone (GH) responses. Although there were no differences between patients and control subjects in the mean decrease in glucose levels after the insulin tolerance test, depressed men demonstrated significantly lower prolactin and GH levels after the test.

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Several neuroendocrine-provocative tests have been used to demonstrate functional alterations in hypothalamic-pituitary target organ responsiveness in patients with major depression (1-12). In addition, peripheral hormonal response abnormalities have been reported in some depressed patients after administration of ACTH (13, 14) and oral glucose loading (4, 15; unpublished 1985 paper of Winokur et al.).

One of the earliest strategies for assessing neuroendocrine dysregulation in depression involved the insulin tolerance test. Most studies have described a blunted growth hormone (GH) response after insulin administration (4-9), but some have also demon-

strated a diminished hypoglycemic response, suggesting the possibility of alterations in CNS neurotransmitter regulation and a relative resistance to insulin (4, 5, 9, 15-17).

Although early reports of a blunted GH response to the insulin tolerance test were intriguing, interpretation of these results has been confounded by a number of methodologic problems. For example, the studies used small patient samples with a relative paucity of age- and sex-matched control subjects, and there was often diagnostic heterogeneity in the patient samples as well as varying definitions of "blunted" GH responses.

Sachar et al. (5) reported that five of 13 patients with psychotic, neurotic, and bipolar depression had a blunted GH response to the insulin tolerance test, but in a subsequent study of eight male and female patients with unipolar depression, five men with bipolar disorders, and nine healthy control subjects (6) they demonstrated a diminished GH response primarily in depressed postmenopausal women. Similarly, a diminished mean GH response to the insulin tolerance test was reported by Mueller et al. (4) in 20 depressive patients, while Gregoire et al. (8) observed a blunted GH response in five of 10 depressed patients. Neither of the latter studies used healthy volunteer control subjects. Finally, Casper et al. (9) administered the insulin tolerance test to 13 depressed patients and an unspecified number of healthy control subjects and observed a diminished peak GH response in depressed men.

In contrast to these studies, preliminary findings from the Collaborative Program on the Psychobiology of Depression of the Clinical Research Branch, National Institute of Mental Health (NIMH) (18), demonstrated no differences in mean GH response after the insulin tolerance test in 54 patients with unipolar depression and 40 healthy volunteer control subjects. These findings were subsequently replicated by two smaller studies from our group (19, 20).

The methodologic limitations of many of the early insulin tolerance test studies, together with conflicting GH results from more recent investigations, suggest the need for more extensive and well-controlled studies using the insulin tolerance test in depression. In this paper we report observations on cortisol, prolactin, and GH responses after the insulin tolerance test in 72 patients with major depression and 51 normal healthy

Received Sept. 27, 1985; revised March 6 and July 9, 1986; accepted Aug. 11, 1986. From the Depression Research Unit, Department of Psychiatry, School of Medicine, University of Pennsylvania. Address reprint requests to Dr. Amsterdam, Depression Research Unit, 1-Gibson, Hospital of the University of Pennsylvania, 36th and Spruce Streets, Philadelphia, PA 19104.

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volunteer control subjects studied under similar conditions.

METHOD

Subjects

Thirty male and 42 female outpatients from the Depression Research Unit at the Hospital of the University of Pennsylvania were studied. The mean \pm SD age of the men was 41 ± 13 years (range=18–68 years); the mean age of the women was 40 ± 11 years (range=18–64 years). All 72 patients had unipolar major depression, either single episode or recurrent, diagnosed according to the criteria of *DSM-III*. In addition, 17 of the 30 men and 26 of the 42 women also fulfilled *DSM-III* criteria for major depression with melancholia. The mean ages of these subgroups of patients were 41 ± 14 years (range=18–68) for the men and 42 ± 12 years (range=22–64) for the women.

All of the patients scored at least 18 on the 17-item Hamilton Rating Scale for Depression (21). The mean Hamilton score of all 30 depressed men was 25.8 ± 5.4 ; for the 42 depressed women it was 24.5 ± 4.1 . For the subgroup of patients with major depression with melancholia, the mean Hamilton score for the 17 men was 28.9 ± 4.3 and for the women was 26.4 ± 3.7 .

Patients with characterologic and dysthymic disorder and patients with manic-depressive (bipolar I) disorder were specifically excluded from this study. All subjects included had been drug free for a minimum of 10 days before testing; most had been drug free for 2 weeks or longer. No patient had ever received a slow-release neuroleptic, and none had received either a standard neuroleptic, protriptyline, lithium carbonate, or ECT within 6 months of testing. In addition, patients were without physical illness and had no clinically significant laboratory abnormalities. None had a past history of endocrinopathy or major medical illness, and all subjects were within 20% of their ideal body weight. None of the women was taking oral contraceptive agents.

Twenty-four male and 27 female drug-free healthy volunteers were also tested under similar conditions. The mean \pm SD age of the male control subjects was 31 ± 10 years (range=21–56 years). These men were significantly younger than all 30 male patients with major depression ($t=2.9$, $df=52$, $p=.005$) and the 17 male patients with major depression with melancholia ($t=2.7$, $df=39$, $p=.005$). The mean age of the 27 female control subjects was 38 ± 12 years (range=23–60 years).

All of the control subjects were given a semistructured psychiatric interview and were free of psychiatric illness according to *DSM-III* criteria. All were free of medical illness, and none had a past history of endocrinopathy or corticosteroid use. Furthermore, none had a family history of major psychiatric illness in either a primary or a secondary relative.

All patients and control subjects participated in the study after providing written informed consent.

Procedure

Tests were performed at 8:30 a.m. after an overnight fast. Premenopausal women were studied at any point in their menstrual cycle. A 19-gauge indwelling venous needle with an attached three-way stopcock was inserted into an antecubital arm vein, and a slow infusion of 0.9% normal saline was started to keep the vein open. Baseline blood samples for glucose, cortisol, prolactin, and GH were collected 15 minutes before testing and immediately before testing. Crystalline synthetic (glucagon-free) regular insulin, 0.1 U/kg, was then injected as an intravenous bolus, and blood samples were obtained at 10, 20, 30, 40, 50, 60, and 75 minutes after injection for determination of glucose, cortisol, prolactin, and GH concentrations in serums. We employed a criterion of a postinsulin glucose decrease of at least 50% of the fasting level for inclusion in the hormonal data analyses; this criterion has been used in previous studies (5–9). Two subjects were excluded from all analyses for this reason: one man with melancholic depression and a glucose decrease of 10%, and one nonmelancholic female patient with a glucose decrease of 17%. Data on these two patients do not appear in this report. We elected, however, to retain the data for two patients with glucose decreases of only 47% who also demonstrated a GH response of 5.6 ng/ml and 11.6 ng/ml as well as data for two patients with a glucose decrease of only 48% and GH responses of 16.1 ng/ml and 51.8 ng/ml. Although the criterion of 50% reduction in glucose is usual, the magnitude of glucose decrease necessary to achieve a maximum GH response appears variable and has not been conclusively demonstrated (22).

Glucose concentrations were measured by using glucose-oxidase-derived techniques (23). The levels of other hormones were determined by radioimmunoassay techniques, as described previously (19, 24). Assays were simultaneously performed on samples from patients and control subjects. All samples from a single subject were assayed together in duplicate.

The term "basal" is used to refer to the hormone concentrations obtained immediately before the administration of insulin. The maximum decrease in glucose below fasting levels was measured, representing the basal minus the lowest value. For cortisol, prolactin, and GH, the maximum increase of hormonal release above the basal value was measured, which represented the peak minus the basal concentration.

Subjects with basal cortisol and prolactin levels beyond two standard deviations of the control mean or with basal GH concentrations of 5 ng/ml or greater were excluded from the data analysis for that particular hormone. Any subject with a basal fasting glucose concentration above 100 mg/dl was excluded from all data analyses. As a result, one female and one male

TABLE 1. Glucose and Hormone Levels of Depressed Patients and Normal Control Subjects Given Insulin Tolerance Test

Subjects	N	Glucose						N	Cortisol				N	Prolactin			
		Basal Level (mg/dl)		Maximum Decrease (mg/dl)		% Change	Basal Level (μg/dl)		Maximum Increase (μg/dl)		Basal Level (ng/ml)			Maximum Increase (ng/ml)			
		Mean	SD	Mean	SD		Mean		SD	Mean	SD	Mean		SD	Mean	SD	
Control subjects																	
Men	24	86	7	60	8	70	9	24	10.6	5.6	19	16	23	14.4	5.6	28	26
Women	27	87	8	60	9	69	9	25	12.3	5.3	16	7	22	23.5	17.5	36	34
All patients with major depression																	
Men	30	91	12	60	10	67	10	25	13.9	6.5	15	8	28	11.6	4.4	14 ^a	23
Women	42	84	12	57	10	67	10	37	10.5	4.1	19	8	38	19.7	10.9	24	40
Subgroup of patients with melancholic subtype																	
Men	17	91	12	59	11	66	9	15	14.6	7.4	14	9	16	11.7	5.4	18	30
Women	26	83	11	56	11	68	9	23	11.3	4.1	20	8	25 ^c	17.6	8.8	29	47

^aSignificantly lower than control subjects ($t=2.1$, $df=42$, $p=.04$).

^bSignificantly lower than control subjects ($t=2.2$, $df=50$, $p=.035$).

^cSignificantly lower than control subjects ($t=2.6$, $df=67$, $p=.013$).

^dSignificantly lower than control subjects ($t=2.7$, $df=37$, $p=.01$).

^eMaximum increase, $N=24$.

^fNonsignificantly lower than control subjects ($t=1.9$, $df=51$, $p=.058$).

patient and one male control subject were excluded from the final GH analyses. This procedure allowed for statistical analyses with normal, untransformed data.

The mean basal, maximum decrease of glucose, and maximum increase of hormonal concentrations were compared by using Student's t test. The change over time was examined by using a two-way analysis of variance (ANOVA) with repeated measures. Analyses were performed separately for healthy control subjects, for the entire group of patients with major depression, and the subgroup of depressive patients with melancholic subtype.

Interrelationships between the basal glucose, maximum decrease in glucose, and percent fall in glucose after the insulin tolerance test; the basal and maximum increase values for cortisol, prolactin, and GH; and age and severity of illness were examined by using Spearman's rank-order correlation test.

RESULTS

The data for men and women were analyzed separately. In addition, we performed a nosologic separation of patients into all those with major depression and those with the melancholic subtype. We felt that this represented a heuristic approach to increasing "biochemically" defined depression. Furthermore, we anticipated that neuroendocrine abnormalities not well defined in the entire group of patients with major depression might become more evident in the melancholic patients.

Basal concentrations of glucose, cortisol, prolactin, and GH for patients and healthy control subjects are displayed in table 1. A significantly lower basal GH

concentration was observed in all depressed women compared with their controls (table 1), and there was a trend for lower basal GH levels in the subgroup of female patients with melancholia compared with their controls.

There were no significant differences in basal concentrations of glucose, cortisol, prolactin, or GH between depressed and healthy men (table 1).

Because hormonal responses to insulin may be partly determined by the overall percentage of hypoglycemia (22, 25–27), we standardized individual variations in basal and maximum decrease in glucose concentrations by determining the total percent of decrease after insulin administration. When this was performed we observed a similar mean hypoglycemic response for patient and control groups.

The mean maximum increase in hormonal values after the insulin tolerance test are displayed in table 1. There were no differences in glucose decrease between any patient group and sex-matched control subjects. The glucose nadir occurred by 30 minutes in all groups.

The maximum increases in prolactin responses were diminished in both groups of depressed women; however, they failed to reach statistical significance due to the large variance in basal and maximum increase in prolactin after the insulin tolerance test (table 1). Sampling at different times during the menstrual cycle may have contributed to this variance (27, 28). The mean maximum increase in prolactin, however, was significantly lower in all depressed men than in their healthy controls (table 1).

Although the mean increase in GH after the insulin tolerance test was significantly lower for the entire group of depressed men than for their controls (table 1), the difference was even greater for the melancholic

N	GH			
	Basal Level (ng/ml)		Maximum Increase (ng/ml)	
	Mean	SD	Mean	SD
23	2.1	0.7	30	24
27	3.1	1.8	30	25
29	2.0	1.1	26 ^b	17
41	2.1 ^c	1.5	27	18
16	2.0	1.1	20 ^d	13
26	2.2 ^f	1.7	31	18

male subgroup compared with their controls (table 1).

More detailed analyses were performed by using a two-way ANOVA with repeated measures over time. As expected, insulin produced a highly significant decrease in glucose concentration by 30 minutes in both the depressed and healthy women; no between-groups difference was observed. However, significantly less hypoglycemia was produced after insulin in the entire group of depressed men compared with their controls ($F=3.9$, $df=1,52$, $p=.05$), and there was a similar but nonsignificant trend for the melancholic men ($F=3.3$, $df=1,39$, $p=.073$).

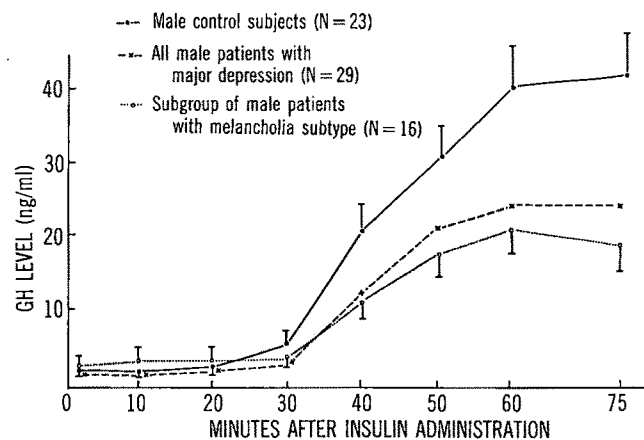
Although insulin produced a significant mean rise in cortisol over 75 minutes in all subject groups ($p<.001$), no differences were observed between any of the patient groups and their sex-matched controls.

Interestingly, although the entire group of men with major depression demonstrated a significant blunting of prolactin response compared with their controls ($F=5.5$, $df=1,49$, $p=.022$), the subgroup of male patients with melancholia did not. In addition, there were no differences in the prolactin response to the insulin tolerance test between the groups of depressed women and their healthy controls.

Insulin produced a greater than tenfold increase in mean GH concentrations in all subject groups ($p<.001$). In addition, the entire group of depressed men demonstrated a significantly lower GH response compared with their controls ($F=9.45$, $df=1,50$, $p=.004$), and the melancholic men had an even more profound blunting of GH response ($F=10.02$, $df=1,37$, $p=.003$) (figure 1). Although insulin produced a significant rise in GH levels in depressed and healthy women ($p<.001$), there were no differences between the groups.

We examined correlations between basal concentra-

FIGURE 1. Release of GH in Depressed Male Patients and Normal Control Subjects Given Insulin Tolerance Test



tions of glucose, cortisol, prolactin, and GH and the percent change in glucose and the maximal glucose decrease after insulin; the maximum increase in cortisol, prolactin, and GH; age; and severity of illness as determined by Hamilton scale scores. The correlations are shown in table 2. A significant correlation was observed between basal glucose levels and the maximum glucose decrease after the insulin tolerance test in all subject groups. In addition, the percent change in glucose levels was positively correlated with the maximum increase in prolactin levels in both groups of depressed men and with the maximum increase in GH levels in the subgroup of melancholic men. Furthermore, the maximum increase in prolactin levels was significantly correlated with the maximum increase in GH levels in all patient groups but not in healthy control subjects. Finally, no significant correlations were observed between the severity of illness or age and any of the basal or insulin-induced levels of glucose or hormones.

DISCUSSION

The results of this study are in partial agreement with those from previous studies using smaller patient samples (4–9). Sachar et al. (5–7) reported a diminished GH response in postmenopausal women with unipolar depression, but Casper et al. (9) observed a lower maximum increase in GH response in both men and women. In addition, Mueller et al. (4) reported a lower GH response in more severely ill patients, and Kleesiek et al. (29) observed a lower GH response in patients with endogenous depression compared with patients with reactive depression and healthy control subjects.

In the present study, the mean GH response to the insulin tolerance test was significantly lower in the men with major depression ($p=.035$) and even more profoundly blunted in the melancholic men ($p=.01$) (figure 1), but GH release was similar in depressed and

TABLE 2. Significant Spearman Correlations Between Basal Levels and Insulin-Induced Changes in Glucose and Hormone Levels in Depressed Patients and Normal Control Subjects

Subjects	Glucose—Maximum Decrease		Glucose—% Change		Cortisol—Maximum Increase		Prolactin—Maximum Increase		GH—Maximum Increase	
	Correlate	r_s	Correlate	r_s	Correlate	r_s	Correlate	r_s	Correlate	r_s
Control subjects										
Men	Basal glucose level	.42 ^a								
Women	Basal glucose level	.45 ^a	Maximum cortisol increase	.51 ^a						
All patients with major depression										
Men	Basal glucose level	.56 ^b	Maximum prolactin increase	.44 ^a			Maximum GH increase	.40 ^a		
Women	Basal glucose level	.68 ^b			Maximum GH increase	.38 ^a	Maximum GH increase	.54 ^b		
Subgroup of patients with melancholia										
Men	Basal glucose level	.54 ^a	Maximum prolactin increase	.54 ^a			Maximum GH increase	.51 ^a	Glucose % change	.70 ^c
Women	Basal glucose level	.66 ^b					Maximum GH increase	.51 ^b		

^a $p < .05$.^b $p < .002$.^c $p < .01$.

healthy women. These findings contrast with those from a previous study by our group (19, 20) in which we observed a similar GH response in both depressed men and women compared with control subjects. Although the reason for this discrepancy is not immediately clear, one possible explanation might be the smaller number of patients in these studies (19, 20). In addition, variability in hormonal response to the insulin tolerance test may also be influenced by differences in the clinical and demographic characteristics of patient samples (22, 25–27, 30), a possibility supported by the observation that healthy volunteers demonstrate a high degree of variability in GH response after repeated insulin tolerance tests (22).

Several investigators have also reported a blunted hypoglycemic response to insulin in depressed patients (4, 5, 9, 15–17), an observation suggesting the possibility of a functional alteration in insulin receptor sensitivity (31, 32). However, in the present study, we did not demonstrate a relative blunting of the hypoglycemic response to insulin in depressed patients.

Nathan et al. (32) have speculated that the reduced GH response to the insulin tolerance test in some depressed patients might result from elevated serum cortisol causing a relative insulin receptor subsensitivity. Although this possibility is intriguing, our observations do not support this hypothesis, in that we found no difference in basal cortisol levels in patients and control subjects, nor did we find any correlation between basal cortisol concentrations and maximum increase in GH levels.

We observed a significantly diminished prolactin response in the entire group of men with major depression ($p = .04$) and a trend for lower prolactin response in the melancholic men as well as in both groups of depressed women. These observations confirm our previous findings in bipolar depressed men given the insulin tolerance test (20) as well as in studies of depressed patients given apomorphine (33), methadone (34), and thyrotropin-releasing hormone (TRH) (24). In addition, the large variability in prolactin response that we observed has been reported previously (19, 20, 24, 35) and may have contributed to the lack of statistical significance in the groups of melancholic men and depressed women.

Because of the influence of diagnostic heterogeneity, it seemed reasonable to designate separate patient groups representing increasing diagnostic refinement in order to assess neuroendocrine responses to the insulin tolerance test as a potential biological marker for depressive illness (36). Although we anticipated that the melancholic subgroup would demonstrate more profound endocrine abnormalities than the entire group of patients with major depression, this was not invariably the case. Only the GH response in men became progressively abnormal with increasing diagnostic homogeneity (figure 1).

Finally, the mean age of the depressed men was slightly, but significantly, greater than that of the healthy men, and separate comparisons were performed for all men 45 years of age or younger. Because results were similar to those seen in the entire group of

men, we concluded that the diminished GH and prolactin response in the depressed men was not simply a function of age.

In summary, the subtle nature of neuroendocrine dysregulation in depressive illness makes it difficult to identify a consistent abnormality in hormonal response to neuroendocrine challenge tests. The combination of an inherently large hormone response variance and the subtlety of the endocrine dysfunction in depression provides an explanation for the inconsistencies seen in previous studies using the insulin tolerance test. Further investigations with large, well-defined patient samples will be necessary to fully appreciate the potential use of the insulin tolerance test in assessing neuroendocrine disturbances in affective disorders.

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AIDS Antibody Tests on Inpatient Psychiatric Units

Renée L. Binder, M.D.

An antibody test for the causative virus of the acquired immune deficiency syndrome (AIDS) became commercially available in 1985. The author discusses the use of the AIDS antibody test on inpatient psychiatric units. She reviews the controversial legal and ethical questions related to its use, addressing such questions as Who should be tested for the AIDS antibody? When and to whom should the results of the test be disclosed? and How should the doctrine of "right to privacy" be balanced with the "duty to warn"?

(Am J Psychiatry 1987; 144:176-181)

Acquired immune deficiency syndrome (AIDS) is a serious disease that affects the immune system. Patients with AIDS become susceptible to a variety of infections and malignancies that ultimately cause their death. It is a frightening disease because it is transmissible, has no cure, and has a long incubation period—between 6 months to more than 5 years—so that infected individuals may not manifest the disease for a long time. Although first reported in 1981, AIDS has occurred in the United States since 1978 (1, 2). During 1984, the causative virus, human T-lymphotropic virus-type III (HTLV-III), was discovered and a test was developed to detect antibodies to the virus (3). This test was originally used for research purposes and in blood banks to keep the AIDS virus out of the blood supply. In 1985, the AIDS antibody test became commercially available, and we were able to request it for patients hospitalized on our acute inpatient psychiatric unit. This paper represents, to my knowledge, the first report in the literature that discusses the use of the AIDS antibody test on an inpatient psychiatric unit and legal and ethical issues related to its use.

The situation with patients who are seropositive for AIDS antibody is different from that for patients who have been diagnosed as having AIDS. First, patients with the AIDS virus antibodies often seem physically healthy and may not know that they have antibodies to

the AIDS virus (4). In contrast, when we have had patients with AIDS on our psychiatric unit, these patients often knew or suspected that they had AIDS before admission because many of them had recurrent physical illnesses. Second, patients with positive antibody tests may never get AIDS. Preliminary estimates in cohorts of homosexual men followed prospectively for 2–5 years indicated that only between 5% and 20% of persons with detectable HTLV-III antibodies go on to develop AIDS (1). In addition, there may be some false positives (5). Therefore, the significance of a positive antibody test is not clear in terms of whether a patient will ultimately develop AIDS. Third, there is evidence that patients with the AIDS antibody may be more infectious than patients who have full-blown AIDS. The reason for this is that there are larger quantities of virus in their blood. In contrast, it may be difficult to isolate the virus in patients with late-stage AIDS (6). Fourth, AIDS is considered a reportable infectious disease and is routinely reported to state departments of public health. In contrast, the names of patients with positive AIDS antibodies are not reported in any state except Colorado (7). Moreover, there is specific California legislation mandating the confidentiality of the results of the AIDS antibody test. This will be discussed further.

Because of the differences between patients with AIDS and patients with positive AIDS antibodies, there are additional legal and ethical dilemmas that arise in the management of patients with AIDS antibodies compared with the management of patients with AIDS. These include the questions, 1) Which patients should be tested for the AIDS antibody? 2) Should staff be screened for the AIDS antibody? 3) Should the results of the AIDS antibody test be held confidential from staff, other patients, sexual partners, outpatient facilities, and hospitals accepting transferred patients? and 4) What admission and management decisions should be made regarding patients with positive AIDS antibody test results? Each issue will be discussed separately and examples will be given.

WHICH PATIENTS SHOULD BE TESTED?

To assist local and state health departments to respond to the licensure of the HTLV-III antibody test, a national meeting of epidemiologists, physicians, representatives of health departments, gay rights groups,

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blood banks, and staff of the Centers for Disease Control (CDC) was convened in March 1985 to develop national guidelines for the use of this test. The resulting guidelines (8) stated that the test is of value for screening donated blood and in some clinical and research situations as an adjunctive diagnostic test. In addition, the guidelines stated that the test is useful in distinguishing whether someone in a high-risk group (homosexual and bisexual men, intravenous drug users, patients with hemophilia, and sexual partners of individuals in these groups) has or has not been infected with the virus.

The gay community in San Francisco has organized counseling sessions to advise people as to whether they should have the HTLV-III antibody test, which is available at various testing sites throughout the city. Reasons for having the test include relieving anxiety about whether one has been infected with the virus and, if the test is positive, to avoid transmission to others. The CDC has stated that prevention of AIDS depends on early identification of infected persons (1). There are also arguments against having the test. One such argument is the fact that only a small percentage of people with positive antibodies will get AIDS and, therefore, a positive test result will cause a great deal of anxiety which may turn out to be unfounded. Another argument against having the test is that there are false positives and, therefore, the significance of a positive test may be misinterpreted—i.e., a positive test result will cause unwarranted anxiety. Individuals may react to a positive test result as they would to a diagnosis of AIDS, i.e., with disbelief, numbness, denial, anger, and acute turmoil, along with disruptive anxiety, depressive symptoms, fear, embarrassment, and guilt feelings (9–11). An additional argument against the test is that it may be used for discrimination purposes. Even though the results of the test are supposed to be confidential, it is impossible to say that anything is totally confidential because if information is available, someone may get access to it. If employers or insurers had access to the information, they might discriminate against the individual. There have been reports of landlords evicting tenants suspected of carrying the illness, hospital unions seeking to exclude persons with AIDS from medical care, and morticians refusing to handle the bodies of patients who have died from AIDS (11). Therefore, according to this argument, it is better not to have the test in the first place. Another argument is that the test is unnecessary for public health reasons because individuals in high-risk groups should be using “safe sex” practices (e.g., use of condoms) anyhow; therefore, they do not need to know the test results.

The legal issues regarding protection of the population from compulsory testing involve the constitutional right to privacy. Forced testing for epidemiologic studies would result in the invasion of bodily integrity by drawing blood and disseminating information on test results to health personnel and epidemiologists. The right to privacy is not specifically men-

tioned in the U.S. Constitution, but, in a line of decisions going back to 1891, the Supreme Court has recognized a fundamental right of personal privacy relating to activities concerning areas such as marriage, procreation, contraception, and family relationships. When government action is directed against an individual's fundamental rights, the Supreme Court has held that it may be justified only by a “compelling state interest” (12). In the case of AIDS antibody testing, there was “urgency” legislation passed in California stating that AIDS antibody testing must be voluntary and that patients must give specific written consent. Thus, in California, legislators have decided that “compelling state interest” does not exist for this procedure.

On our inpatient psychiatric unit, most patients are acutely psychotic. The question arises, When, if ever, should the HTLV-III antibody test be ordered? The argument for ordering the test is that when psychotic patients in high-risk groups display out-of-control behavior, they may not have control of their own secretions; if their saliva, blood, urine, or feces contain the AIDS virus, this information should be available for the protection of staff and patients.

An example of this situation was the case of a 19-year-old bisexual man with a history of intravenous amphetamine use who was admitted to our unit in an agitated and paranoid state. During the first 24 hours of hospitalization, he became increasingly physically intrusive and verbally abusive and was placed in seclusion. One hour later, while in seclusion, he began picking his nose until it bled and smeared his blood over much of the seclusion room window and walls.

According to California Assembly Bill 403 (codified in the California Health and Safety Code, Section 199.22), patients need to give specific written consent before the test for AIDS antibodies can be done. The patient described was obviously in no condition to give consent. Therefore, the staff, assuming that because he was in a high-risk group his blood could be positive for the HTLV-III antibody, used infection control precautions in cleaning the patient and the seclusion room. The question can be asked, Should all patients in high-risk groups be managed as if their secretions had the AIDS virus?

Another reason for having the test is for diagnostic purposes. In some AIDS patients, psychiatric disturbances can be striking and can represent the initial presentation of the syndrome. Dementia or severe psychopathology that mimics functional syndromes such as depression, mania, personality change, and psychotic disorganization may precede the medical diagnosis of AIDS (13, 14). There are also several encephalopathies secondary to opportunistic infections or HTLV-III infection that may present with psychiatric symptoms. Approximately 39% of all patients with AIDS have neurological symptoms, and 73% of patients with AIDS have shown pathological abnormalities of the CNS at autopsy (2).

In summary, the arguments for having patients in high-risk groups take the HTLV-III antibody test while

hospitalized on an acute inpatient unit are diagnostic assessment, education of patients about whether they have an infectious disease, and education of staff to take extra precautions with the patient's secretions. The arguments against having patients in high-risk groups tested for HTLV-III antibody while hospitalized on an acute inpatient unit are that patients are already psychiatrically disabled and under stress and it is harmful to add to their stress with the information that they might have a fatal disease, that patients should be educated about "safe sex" practices even if they do not test positive for the AIDS antibody, and that staff should take extra precautions with all patients in groups at high risk for AIDS and all other patients who are unable to control their secretions or excretions.

In any event, according to California law patients must give written consent before the AIDS antibody test can be done. If the patient is unable or unwilling to give consent, staff should treat the patients' secretions as if they were infectious. Tests for hepatitis can be done without the patients' consent, and this information can be useful because there is a correlation between patients who have had hepatitis and patients who have been exposed to the AIDS virus (15).

SHOULD STAFF BE TESTED?

The issue of testing high-risk patients for the AIDS antibody raised the question of testing staff on our unit who are members of high-risk groups. Despite the fact that there is no scientific evidence for the transmission of AIDS through casual contact (16), some administrative personnel felt that testing might be indicated because staff members work in close quarters with each other and have close contact with patients. For example, staff share one bathroom, share their food with each other, and help serve food to patients. These fears were exacerbated when a member of our nursing staff died suddenly and unexpectedly of disseminated cryptococcal meningitis. Subsequently, staff were informed that the nurse had been previously diagnosed with AIDS but did not tell anyone at work. There were many fears about whether he had been infectious while working.

Hospital legal counsel has advised us that there is no authority to test staff involuntarily for AIDS antibody. Testing for AIDS antibody is voluntary and the results are absolutely confidential to protect the employee against job discrimination. Legal counsel has stated, for example, that a supervisor who knows that an employee has AIDS and sees that employee drinking out of the same cup as a pregnant employee is not entitled to say anything. The rationale is that there is no evidence, to date, of transmission of AIDS by casual contact or through saliva (16).

On our psychiatric inpatient unit, we feel that it is ethically as well as legally appropriate to refrain from encouraging staff to have the AIDS antibody test. This

is because we assume that staff members have control of their own secretions. In addition, there is no proof of spread of AIDS through casual contact. Moreover, we do not want to encourage isolation and estrangement of the employee whose test result for the AIDS antibody is positive.

ISSUES CONCERNING CONFIDENTIALITY

California Assembly Bill 403 (codified in the California Health and Safety Code, Section 199.21) specifically prohibits the disclosure of the results of the AIDS antibody test without written consent of the patient. The law states that written authorization is required for each separate disclosure of the test results and shall include to whom the disclosure would be made. Negligent disclosure will result in a civil penalty of up to \$1,000 plus court costs. Willful disclosure will result in a civil penalty of \$1,000 to \$5,000 plus court costs. Willful or negligent disclosure that results in economic, bodily, or psychological harm to the subject of the test is a misdemeanor punishable by imprisonment in the county jail for up to 1 year, a fine of up to \$10,000, or both. Each disclosure is a separate and actionable offense. Disclosure means to disclose, release, transfer, disseminate, or otherwise communicate all or any part of any record orally, in writing, or by electronic means to any person or entity.

Should Results Be Disclosed to Staff?

The treating inpatient physician may gain knowledge that a patient has a positive AIDS antibody test result, either through a test done on our unit with the patient's consent or because the patient had a previous test and notified the physician of the results. We asked our legal counsel whether this information could be divulged to the rest of the staff and whether the results should be in the open medical record that is used as a means of communication among staff members. At some of the outpatient testing sites, anonymity and confidentiality are preserved by identifying patients only by a number. When patients call for their results, they need to give only their number, so that none of the staff will know who they are. On an inpatient unit, the situation is different because all the staff work closely together to provide a coordinated treatment plan. Legal counsel advised us that the inpatient treating physician can disclose the test results to the rest of the staff because the entire staff is considered one treatment unit.

Should Results Be Disclosed to Other Patients?

When the inpatient unit staff knows that a patient has an infectious disease, such as hepatitis, we post signs that infection control precautions apply to the patient. Other patients, of course, notice that the patient gets special treatment, such as having his or her

own tray at mealtime. When the subject is discussed at patient community meetings, we explain that precautions are taken with the patient and that the details of his or her illness are confidential. We follow the same procedure when a patient has a positive AIDS antibody test result, i.e., the infection control precautions are taken and the details of the patient's illness are confidential. The situation, however, can become much more complicated with reference to confidentiality of the results of the AIDS antibody test.

An example of this situation was the case of a 22-year-old heterosexual, married man with a diagnosis of paranoid schizophrenia. While being evaluated for management of agitation and increased delusional ideas, he suddenly ran out of the interview room, which is located on the unit, and bit another patient on the cheek, drawing blood. The bitten patient had had a positive AIDS antibody test result.

The question was raised as to whether we should tell the paranoid schizophrenic patient that he had come in contact with a small amount of the blood of a patient with positive AIDS antibody. On the one hand, did he not have the right to know that he might have contracted a fatal disease? On the other hand, as evidenced by the studies on venipuncturists who have stuck their fingers with contaminated blood and not contracted AIDS (16), the likelihood of the patient's contracting AIDS was minimal. In addition, this knowledge would have made him extremely anxious and might have worsened his psychiatric condition. According to California law, we were bound not to disclose information about the AIDS antibody test to another patient. However, there are lawsuits claiming liability and negligence for transfusion of AIDS-contaminated blood (17). Could this be extended to lawsuits about staff responsibility to prevent one patient from giving the AIDS virus to another patient? A related issue is whether we have a "duty to warn." In accordance with this duty, blood banks are notifying recipients of blood products from donors who subsequently develop AIDS and from donors who are HTLV-III positive.

Should Results Be Disclosed to Sexual Partners?

The names of patients who have laboratory test results indicating that they have a venereal disease are given to the public health department. The department contacts the patients to obtain a list of their sexual contacts. The sexual contacts are then notified that they may have been exposed to an infectious disease (the name of the index patient is not divulged) and are advised to come for testing and treatment. AIDS is also a reportable disease, and there is statutory authority to notify the sexual contacts of the index patient. In San Francisco, because of logistical difficulties contacts are not notified in the cases of homosexual men. However, contacts are notified when there may be heterosexual transmission. The situation with a positive AIDS antibody test is different because the results must be kept

confidential. When the positive test results are known to the treating psychiatrist, there are some complicated legal and ethical choices, as illustrated by the following example.

A 23-year-old bisexual man was admitted for depression and suicidal ideation. He was living with a woman, and they had an active sexual relationship. During his hospitalization, he asked to have the AIDS antibody test; the results were positive. He did not want this information given to his girlfriend. We were prohibited by law from divulging this information to the patient's girlfriend. Yet, we were also very aware of the issues raised in the *Tarasoff* decision in California (18) whereby we are required to warn potential victims. Although the *Tarasoff* decision referred to victims of violence, we wondered whether that could be extended to other types of victims. In fact, in a recent Supreme Court decision in Vermont (19), the court used the issue of duty to warn about cases of venereal disease as one of the rationales for duty to warn about violence: "Physicians, health officials and health institutions are required, in patient cases of venereal and other contagious diseases, to warn others in order to protect the public health. We see no reason why a similar duty to warn should not exist when the 'disease' of the patient is a mental illness that poses an analogous risk of harm to others" (p. 4). With reference to our patient with his girlfriend, we wondered about our liability if the patient transmitted AIDS to his girlfriend and she died. Would we not be liable for not warning her of this potential danger? A related issue is a potential wrongful birth or wrongful life suit. If the girlfriend became pregnant and delivered an infant with AIDS, would there be liability? Would the hospital be responsible for paying for medical care for the infant? There are obviously two legal doctrines in conflict in the attempt to decide about divulging information related to the AIDS antibody test. One refers to confidentiality of the AIDS antibody test and one refers to warning potential victims. This conflict will have to be resolved by the courts as the result of a lawsuit or by additional clarifying legislation.

Should Results Be Disclosed to Medical Facilities?

California law specifically addresses the issue of whether to disclose the results of the AIDS antibody test to outpatient facilities when patients are referred for ongoing treatment. Clearly, these results should not be disclosed to outpatient facilities. At our hospital, information about the AIDS antibody test is not included in the discharge summary. In addition, if outpatient facilities request copies of the patient's chart, references to the AIDS antibody test are deleted unless we have specific written consent for disclosure from the patient.

Another related question is, Should the results of the AIDS antibody test be disclosed to hospitals accepting transferred patients? An example of this situation was the case of a 21-year-old patient with hemophilia who

developed psychotic symptoms and agitation. He had a positive AIDS antibody test result. The differential diagnosis included AIDS encephalopathy and paranoid schizophrenia. With neuroleptic medication, his agitation decreased but his delusional ideas continued, and we felt that he needed longer-term hospitalization in a subacute facility. The question arose as to whether we were permitted to notify the subacute facility that he had a positive AIDS antibody test result. According to the law, we were not permitted to divulge this information. Yet, it somehow seemed inappropriate to attempt to transfer a patient to another facility without giving the facility a complete medical history, including the information that the patient possibly had infectious secretions (the patient bled easily) and that his current or future psychiatric symptoms might be related to infection with the HTLV-III virus. Legal counsel recommended that we not divulge information about the AIDS antibody test because it was not legal to do so. Instead, the referring physician kept emphasizing that the patient had hemophilia and hoped that the physician accepting the transfer would realize the significance of this history (almost all patients with hemophilia in the San Francisco Bay area have received HTLV-III-infected blood).

ADMISSION AND MANAGEMENT DECISIONS

It has been reported that patients with AIDS evoke a high level of tension, fear, and uncertainty among psychiatric staff (20, 21). This is also true of patients with positive AIDS antibody tests.

An example of this situation was the case of a 20-year-old patient with hemophilia who was transferred from the hematology service to the psychiatric unit because of unmanageable behavior. He had a positive AIDS antibody test result and was delusional about being the King of England. After transfer to our unit, his agitation increased and he was unresponsive to neuroleptic and sedative hypnotic medications. Management issues related to the patient's hemophilia involved how to restrain him when he was banging his head against the wall and at the same time prevent or minimize bruising. Also, when he refused oral medications, staff were reluctant to give him intramuscular injections, which caused bruising. Management issues related to the patient's positive AIDS antibody status included the questions, Was the patient's blood infectious? If the patient's agitation was due to untreatable AIDS encephalopathy, would he need to be in seclusion and restraint on an ongoing basis? Would there be adequate funds to pay for additional nursing staff to provide one-to-one supervision for the patient? What if the patient remained psychotic and could not be discharged or transferred to another facility, i.e., what if the patient needed to remain on the unit for the foreseeable future? If the patient developed severe medical complications, would the transfer to a medical facility be delayed due to AIDS-related concerns?

The patient remained on the psychiatric unit for several months (the average length of stay on the unit is 2 weeks) with the diagnosis of probable AIDS encephalopathy. During his hospitalization, staff was increased so that the one-to-one contact with the patient could be maintained because his behavior was so out of control. Obviously, this patient's hospitalization was quite costly. The pragmatic, although politically controversial, questions are, How many of these patients can be managed by any one unit at any one time? How should it be decided which patients have access to the limited resource of an acute psychiatric bed? Who should pay for the lengthy hospitalization of these patients? In the San Francisco Bay area, it is very difficult to transfer patients to chronic hospital beds if they have a combination of medical and psychiatric problems. If, in addition, patients have a possibly communicable disease, it is practically impossible.

CONCLUSIONS

In this paper I have discussed the legal and ethical dilemmas related to treating patients with positive AIDS antibody tests on an inpatient psychiatric unit. These issues have arisen only recently because the AIDS antibody test has been available only since mid-1985. In addition, these issues have crystallized in California because of the recent passage of "urgency" legislation regarding confidentiality of the test results, signed by the Governor on April 3, 1985. It is clear that the legal and ethical issues related to the treatment of patients with positive AIDS antibody test results are complicated and are not subject to easy resolution. In the future, as the test becomes more widespread, we will continue to be confronted with the legal and ethical issues explored in this paper.

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State and Personality in Depressed and Panic Patients

James Reich, M.D., M.P.H., Russell Noyes, Jr., M.D., Robert Hirschfeld, M.D., William Coryell, M.D., and Tom O'Gorman, M.S.

The authors examined 36 patients with panic disorder, 66 patients with major depression, and 124 control subjects to determine personality differences between them in the ill and the recovered states. The panic and depressed groups did not differ from each other in either state. Both recovered groups had less emotional strength and greater interpersonal dependency than the control subjects. The effect of state on personality measures appears to be similar for anxious and depressed patients. No personality measures that clearly differentiated the recovered panic and depressed patients were found.

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It has been established that both depressive state (1-6) and anxiety state (7) affect personality measures. It has not been established whether state anxiety and

state depression differ in how they affect personality measures and whether there are any personality differences between anxious and depressed patients when the effect of state is removed, that is, in the recovered state. The present report focuses on these two issues.

The literature on symptomatic state and personality measures is limited. There are many reports on the effects of depressive state on results with the Maudsley Personality Inventory (1-6), and although one study (8) reported overcoming this difficulty with specific instructions, that result has been disputed (9). Hirschfeld et al. (5, 6) observed the effects of depressive state across a battery of personality instruments. The results indicated that the depressive state affects measures of emotional strength, interpersonal dependency, and extraversion. It does not appear to affect measures of rigidity, level of activity, and dominance. There is also evidence (7) that state anxiety affects personality measures in similar ways. There is a small literature (10-14) comparing the effects of anxiety and depression on personality measures but none comparing these measures in anxious and depressed patients who have recovered.

The literature is unclear on whether depression and anxiety affect personality measures in similar ways and on the similarities of the premorbid personalities of the two groups. This confusion is due to there being no direct comparison of ill and recovered depressed and anxious patients in the literature. This is no doubt due

Received Jan. 13, 1986; revised June 30, 1986; accepted Aug. 18, 1986. From the Department of Psychiatry and Department of Preventive Medicine and Environmental Health, University of Iowa College of Medicine; and the Clinical Research Branch, NIMH, Rockville, Md. Address reprint requests to Dr. Reich, Department of Psychiatry, University of Iowa College of Medicine, 500 Newton Rd., Iowa City, IA 52242.

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to the more chronic course of anxiety patients (15, 16). To our knowledge, this is the first report in the literature making such a comparison.

METHOD

The numbers, mean ages, and sex distributions of the study samples are displayed in table 1. All subjects were white.

The panic disorder subjects for this study participated in the Cross-National Collaborative Panic Disorder Study (J.C. Ballenger et al., work in preparation). All subjects from the University of Iowa site were included. At this site subjects took part in a controlled trial of alprazolam versus placebo for the treatment of panic disorder, for which they signed statements of informed consent. They were volunteers recruited by newspaper advertisement and were screened with the Structured Clinical Interview for DSM-III Disorders (17). All of them met revised *DSM-III* criteria for panic disorder with or without agoraphobia (R.L. Spitzer, J.B. Williams, unpublished paper, 1983) and were experiencing at least one panic attack per week at the time they entered the study. Half of the subjects who completed the 8-week trial received alprazolam (mean dose=5.6 mg/day), and the remainder received placebo.

Personality measures were obtained at baseline and at 6 weeks, as were scores on the Hamilton Rating Scale for Anxiety (18). It was decided, a priori, to designate as "recovered" each panic subject whose Hamilton anxiety score at week 6 was 10 or less. Of the 60 panic disorder subjects who participated in the treatment study, 36 met our criteria for recovery at 6 weeks (see table 1). Their mean±SD ages at onset and duration of illness were 25.8±7.9 and 8.4±8.4 years, respectively. Five (14%) of the patients had no phobic avoidance, seven (19%) had limited avoidance, and 24 (67%) had extensive avoidance (agoraphobia). Fourteen (39%) had each had an episode of major depression at some point in his or her life, and five (14%) were depressed upon entry into the study. Four (11%) had social phobia, and one (3%) had obsessive-compulsive disorder. Information on prior treatment for panic attacks was available for 21 patients; they had received tricyclic antidepressants (N=9, 43%), benzodiazepines (N=13, 62%), neuroleptics (N=3, 14%), and propranolol (N=1, 5%); five (24%) had been hospitalized. Once in the study, 25 (69%) of our 36 patients received alprazolam. The mean±SD Hamilton depression scores were 14.0±6.1 at baseline and 6.6±5.1 at 8 weeks. This was a significant decline ($t=13.5$, $df=35$, $p<.001$).

The depressed patients for this study were participants in the NIMH Clinical Research Branch Collaborative Program on the Psychobiology of Depression. They signed informed consent statements for the collaborative study. The methods of this program have been described elsewhere (19–24). All the depressed

TABLE 1. Number, Age, and Sex of Depressed Patients, Panic Patients, and Control Subjects in Study of State

Group	N	Age (years)	
		Mean	SD
Panic patients			
Men	14	38.0	10.0
Women	22	33.1	6.7
Depressed patients			
Men	21	30.0	12.0
Women	41	33.9	13.5
Control subjects			
Men	51	38.9	18.4
Women	73	37.4	17.5

patients and their control subjects from the University of Iowa site were included. All subjects had major depression according to the Research Diagnostic Criteria (RDC) (21). Patients who had ever experienced schizophrenia, mania, generalized anxiety disorder, panic disorder, or phobias were excluded from this group. For this group the mean±SD age at onset and duration of current illness were 27.6±11.3 years and 32.9±48.7 weeks, respectively. Their mean±SD number of depressive episodes was 7.7±22.9. Fourteen (23%) had histories of alcohol abuse, and six (10%) had histories of drug abuse. Before entering the study, 25 (40%) had been treated with either tricyclic antidepressants or monoamine oxidase inhibitors, 12 (19%) had been given ECT, and 16 (26%) had been hospitalized for depression. At intake the mean±SD anxiety score for these patients was 10.8±5.2, and at recovery it was 6.4±2.9. This was a significant difference ($t=11.0$, $df=61$, $p<.001$). Personality measures were obtained during the initial hospitalization and 1 year later. Those patients who at 1 year had no more than one or two symptoms of depression for an 8-week period according to the LIFE scale (24) were designated recovered. Collaborative study patients were treated with the physician's treatment of choice (almost always a pharmacologic treatment).

The control subjects were also drawn from the collaborative study; each was an acquaintance of a randomly chosen relative of a study proband. The control subjects had no lifetime history of psychiatric disorder according to the RDC. These nonsymptomatic volunteers were seen at one time only—when they were assessed—and were not followed. The personality measures were obtained at this single contact.

The subjects were given the Guilford-Zimmerman Temperament Survey (25), the Lazare-Klerman-Armor Personality Inventory (short form) (26, 27), and the Interpersonal Dependency Inventory (28). The Guilford-Zimmerman Temperament Survey is a self-report measure of 10 emotional traits (general activity, restraint, ascendance, sociability, emotional stability, objectivity, friendliness, thoughtfulness, personal relations, and masculinity). It has been shown to have reliability, internal consistency, and validity by means of the factor analytic method and correlations with

TABLE 2. Personality Scale Scores for Male Panic and Depressed Patients Before Recovery and for Male Control Subjects

Personality Scale	Male Patients Before Recovery				Control Subjects		Age-Adjusted Analysis of Covariance	
	Panic (N=14) (group A)		Depressed (N=25) (group B)		(N=51) (group C)		Significant Difference	p
	Mean	SD	Mean	SD	Mean	SD		
Emotional strength								
Emotional stability ^a	13.0	1.4	10.8	1.1	23.3	0.7	C>A,B	<.0001
Objectivity ^a	14.5	1.4	13.1	1.1	20.7	0.7	C>A,B	<.001
Orality ^b	6.9	0.9	9.2	0.7	3.4	0.5	B>A	<.05
							A>C	<.001
Interpersonal dependency								
Emotional reliance on another person ^c	47.0	2.6	49.5	2.0	36.7	1.3	A,B>C	<.001
Lack of social self-confidence ^a	35.1	2.1	36.2	1.6	27.5	1.1	A,B>C	<.001
Assertion of autonomy ^c	30.6	1.6	27.7	1.2	26.2	0.8	A>C	<.01
Extraversion/introversion								
Sociability ^a	13.0	1.7	13.7	1.3	19.1	0.9	C>A,B	<.01
Restraint ^a	16.3	1.2	16.2	0.9	16.8	0.6		
Thoughtfulness ^a	16.8	1.3	17.8	1.0	17.4	0.7		
Miscellaneous								
General activity ^a	18.4	1.7	15.6	1.3	16.6	0.9		
Ascendance ^a	10.7	1.6	13.3	1.2	15.2	0.8	C>A	<.01
Hysterical pattern ^b	8.9	1.0	9.7	0.8	6.8	0.5	B>C	<.01
Obsessionality ^b	11.4	0.9	11.4	0.9	13.1	0.5	B>C	<.01

^aGuilford-Zimmerman Temperament Survey (25).^bLazare-Klerman-Armor Personality Inventory (short form) (26, 27).^cInterpersonal Dependency Inventory (28).

other psychological tests, and it has been used extensively on normal subjects and psychiatric samples. The Lazare-Klerman-Armor Personality Inventory is a self-report instrument designed to measure three psychoanalytically derived personality types (oral, obsessional, and hysterical). It has been validated by means of factor analytic techniques. The Interpersonal Dependency Inventory is a self-report measure of three aspects of interpersonal dependency (emotional reliance on another person, lack of social self-confidence, and assertion of autonomy). Validation and cross-validation studies have been performed with normal subjects and psychiatric patients (28). These three instruments were chosen for use with the panic disorder patients because of their broad coverage of personality traits.

The criteria for recovery were different for the two groups, since we used the definition of recovery used by the investigators in each study and those studies were not designed with such a comparison in mind. However, these definitions are not inappropriate. Since depression is an intermittent disease, 8 weeks of minimal depressive symptoms is a reasonable criterion. On the other hand, since panic disorder is a chronic disease, a rapid decrease in symptoms over 6 weeks is also a reasonable definition of recovery. Since both definitions of recovery are adequate, it seems appropriate to compare recovered groups.

An analysis of covariance (adjusting for age effects) was run comparing personality measures obtained from patients with panic disorder, depressed patients, and control subjects. The scores obtained from the panic and depressed patients were analyzed when both were ill and when both were recovered.

RESULTS

Tables 2 and 3 show the comparisons of the mean personality scale scores before treatment for the panic and depressed patients and control subjects. Where there were significant differences, the control group always differed from the depressed or panic patients in the "healthy" or "normal" direction. For men (table 2), the patient groups differed in only one of 13 comparisons; the depressed patients scored higher than the panic patients on orality. For women (table 3), there were no scales on which the patient groups differed significantly. Before treatment, patients of both sexes differed significantly from the control subjects on emotional stability, orality, objectivity, emotional reliance on another person, and sociability. The patient groups, regardless of sex, did not differ significantly from the control subjects on restraint or thoughtfulness.

The mean personality scores for the panic and depressed patients after recovery and the control subjects are shown in tables 4 and 5. Where there were significant differences, the control group always differed from the depressed or panic patients in the "healthy" or "normal" direction. For men (table 4), there were no statistically significant differences between the panic and depressed patients on any of the 13 scales administered. For women (table 5), a significant difference occurred on only one scale, general activity, where the score was lower for the depressed patients. The recovered patients of both sexes scored significantly lower than the control subjects on emotional stability and objectivity; they scored significantly higher on orality, emotional reliance on another

TABLE 3. Personality Scale Scores for Female Panic and Depressed Patients Before Recovery and for Female Control Subjects

Personality Scale	Female Patients Before Recovery				Control Subjects (N=73) (group C)		Age-Adjusted Analysis of Covariance	
	Panic (N=22) (group A)		Depressed (N=41) (group B)				Significant Difference	p
	Mean	SD	Mean	SD	Mean	SD		
Emotional strength								
Emotional stability ^a	10.6	1.3	12.6	1.0	20.3	0.7	C>B,A	<.0001
Objectivity ^a	14.5	1.1	14.0	0.8	19.8	0.6	C>B,A	<.0001
Orality ^b	7.5	0.8	8.3	0.6	3.9	0.5	A,B>C	<.001
Interpersonal dependency								
Emotional reliance on another person ^c	48.0	2.0	49.3	1.4	39.8	1.1	A,B>C	<.001
Lack of social self-confidence ^c	38.8	1.9	37.8	1.4	29.2	1.0	A,B>C	<.0001
Assertion of autonomy ^c	25.1	1.3	27.2	0.9	23.4	0.7	B>C	<.01
Extraversion/introversion								
Sociability ^a	14.6	1.4	13.9	1.1	21.0	0.8	C>A,B	<.0001
Restraint ^a	17.3	1.1	17.3	0.8	16.8	0.6		
Thoughtfulness ^a	17.1	1.0	17.0	0.7	16.8	0.6		
Miscellaneous								
General activity ^a	16.1	1.4	13.8	1.0	17.8	0.7	C>B	<.01
Ascendancy ^a	9.6	1.2	11.7	0.9	14.5	0.7	C>A,B	<.01
Hysterical pattern ^b	9.5	0.8	8.4	0.6	7.3	0.4	A>C	<.01
Obsessionality ^b	12.5	0.7	12.5	0.5	12.9	0.4		

^aGuilford-Zimmerman Temperament Survey (25).^bLazare-Klerman-Armor Personality Inventory (short form) (26, 27).^cInterpersonal Dependency Inventory (28).**TABLE 4. Personality Scale Scores for Recovered Male Panic and Depressed Patients and for Male Control Subjects**

Personality Scale	Recovered Male Patients				Control Subjects (N=51) (group C)		Age-Adjusted Analysis of Covariance	
	Panic (N=14) (group A)		Depressed (N=20) (group B)				Significant Difference	p
	Mean	SD	Mean	SD	Mean	SD		
Emotional strength								
Emotional stability ^a	16.2	1.6	11.7	1.3	23.3	0.7	C>A,B	<.0001
Objectivity ^a	15.7	1.5	14.0	1.3	20.7	0.7	C>A,B	<.01
Orality ^b	6.7	0.9	7.3	0.8	3.4	0.5	A,B>C	<.001
Interpersonal dependency								
Emotional reliance on another person ^c	45.8	2.4	45.4	2.0	36.7	1.3	A,B>C	<.001
Lack of social self-confidence ^c	33.9	2.1	33.7	1.8	27.5	1.1	A,B>C	<.01
Assertion of autonomy ^c	29.5	1.6	28.2	1.3	26.2	0.8		
Extraversion/introversion								
Sociability ^a	15.4	1.8	13.2	1.5	19.1	0.9	C>B	<.001
Restraint ^a	16.1	1.2	15.6	1.0	16.8	0.6		
Thoughtfulness ^a	15.6	1.4	16.3	1.2	17.4	0.7		
Miscellaneous								
General activity ^a	19.7	1.7	15.8	1.5	16.6	0.9		
Ascendancy ^a	13.0	1.6	13.1	1.4	15.2	0.8		
Hysterical pattern ^b	9.1	1.0	9.7	0.9	6.8	0.5	A,B>C	<.01
Obsessionality ^b	11.9	0.9	11.6	0.7	13.1	0.5		

^aGuilford-Zimmerman Temperament Survey (25).^bLazare-Klerman-Armor Personality Inventory (short form) (26, 27).^cInterpersonal Dependency Inventory (28).

person, and lack of social self-confidence. There were no significant differences between the patients and control subjects on restraint, thoughtfulness, or obsessionality. The depressed women, once they had recovered, had significantly higher assertion of autonomy scores than the control subjects. The control subjects scored higher on sociability than did the female panic disorder patients and the depressed men and women. Among women, the general activity scores for the control and panic groups were higher than for the depressed group, and ascendancy was higher in the

control subjects than in the panic patients. Among men, the hysterical pattern score was higher in both recovered patient groups than among the control subjects.

DISCUSSION

Some investigators (10, 12) have hypothesized that the predisposing personality differs between anxious and depressed patients. Since it is clear that both state

TABLE 5. Personality Scale Scores for Recovered Female Panic and Depressed Patients and for Female Control Subjects

Personality Scale	Recovered Female Patients				Control Subjects		Age-Adjusted Analysis of Covariance	
	Panic (N=18) (group A)		Depressed (N=40) (group B)		(N=73) (group C)		Significant Difference	p
	Mean	SD	Mean	SD	Mean	SD		
Emotional strength								
Emotional stability ^a	15.5	1.5	14.6	1.0	20.3	0.7	C>A,B	<.01
Objectivity ^a	15.9	1.2	16.0	0.8	19.8	0.6	C>A,B	<.01
Orality ^b	7.6	0.9	6.7	0.6	3.9	0.5	A,B>C	<.001
Interpersonal dependency								
Emotional reliance on another person ^c	46.3	2.1	44.7	1.4	39.8	1.1	A,B>C	<.01
Lack of social self-confidence ^c	36.1	2.1	35.2	1.4	29.2	1.0	A,B>C	<.01
Assertion of autonomy ^c	24.7	1.5	26.9	1.0	23.4	0.7	B>C	<.01
Extraversion/introversion								
Sociability ^a	16.9	1.6	15.1	1.1	21.0	0.8	C>A,B	<.01
Restraint ^a	15.6	1.2	17.8	0.8	16.8	0.6		
Thoughtfulness ^a	17.8	1.1	17.4	0.8	16.8	0.6		
Miscellaneous								
General activity ^a	19.8	1.5	14.4	1.0	17.8	0.7	A,C>B	<.01
Ascendancy ^a	10.5	1.9	12.8	0.9	14.5	0.7	C>A	<.05
Hysterical pattern ^b	9.0	0.8	8.4	0.6	7.3	0.4		
Obsessionality ^b	13.3	0.8	12.3	0.5	12.9	0.4		

^aGuilford-Zimmerman Temperament Survey (25).^bLazare-Klerman-Armor Personality Inventory (short form) (26, 27).^cInterpersonal Dependency Inventory (28).

depression (6) and state anxiety (7) influence personality measurement, questions of differences in premorbid personality can scarcely be resolved by comparing anxious and depressed patients in the ill state. This requires, instead, comparison of patients in the recovered state. It has long been possible to examine recovered depressed patients; effective treatment for depression has been available for some time and the illness itself is episodic. Study of anxious patients in the recovered state presents a greater challenge; the disease follows a chronic course and effective treatments are a more recent development.

Our results indicate that, for the personality measures used in this study, the similarities between panic and depressed patients far outweigh any differences. In fact, in both the ill and the recovered states they are virtually the same. Several possible conclusions can be drawn from this finding. One is that there are personality traits which predispose to illness in both depressed and panic patients and that these are similar in the two groups. It is also possible that personality dimensions on which these patients might be shown to differ were not measured in this study. A third possibility is that the process of being acutely ill, with depression or panic disorder, results in similar alterations of personality.

The question of whether certain personality traits predispose to panic disorder or major depression is important from a public health standpoint and may have clinical significance as well. Parnas et al. (29) have shown that personality traits can remain stable between the ages of 15 and 25. Ultimately, only prospective studies can answer this question. At present there is one such report in the literature, a study by Nystrom and Lindegard (30). They followed up

3,019 subjects after 6 years, obtaining baseline and 6-year measures of Sjöbring personality factors. They found similar personality traits at baseline in the subjects who subsequently developed anxiety disorders and those who developed depression. However, both groups had different personality measurements at baseline from the rest of the sample. Those findings support the predisposition hypothesis.

From our data it is not impossible to say whether other personality measures could have distinguished between the panic disorder and depressed patients. What we can say is that the similarity of the panic and depressed patients in their differences from the control subjects points to broad similarities in personality between patients with panic disorder and those with major depression. This indicates that, regardless of what differences may be found in the future, clinicians and researchers should understand that similarities may well outweigh the differences between these types of patients.

It is not clear whether the change in personality measures during acute illness represents a temporary change in personality or a distortion of reporting caused by the illness. Beck et al. (31) stated that there is cognitive distortion in anxiety, just as there is in depression. Hibbert (32) also documented characteristic ideational components centered around personal danger in panic patients. This is a difficult methodologic question that will require further study.

It is possible that personality abnormalities which persist with recovery may be the result of having experienced a severe emotional illness. This is made less likely by two lines of evidence. The first is the work of Nystrom et al., just cited, indicating similarity in personality before the illness episode. The second is the

finding of differences in personality between recovered unipolar and bipolar depressed subjects, both of whom have had severe emotional illnesses. Murray and Blackburn (13), using the 16PF, found anxiety patients to be more like unipolar depressed than bipolar patients. Hirschfeld and Klerman (5) also found bipolar patients to be more like control subjects than unipolar depressed patients on personality measures.

The finding of no difference in personality measures between recovered depressed and panic patients is pertinent to the question of whether anxiety and depression share a common diathesis. Factor analytic studies (33–35) have successfully differentiated anxiety from depressive disorders. Course of illness has also been shown to discriminate between these conditions (36–39). However, anxiety and depressive symptoms often coexist (40), and “anxious depression” may be a valid nosologic entity (41). Lechman et al. (42) and Weissman et al. (43), in examining the familial relationship of anxiety disorders and depression, found that first-degree relatives of probands having both depression and anxiety disorders had higher risks for both anxiety disorders and depression than did relatives of probands without anxiety. One explanation might be that persons with certain personality traits are more vulnerable to *either* anxiety or depression. If such personality traits are familial, then relatives of probands with a large loading of these traits might also develop these traits. These relatives would then be at greater risk of developing either anxiety or depressive disorders by virtue of personality characteristics. Characteristics of this kind might assort independently of genetic loadings for anxiety and depression. This hypothesis is consistent with the findings of Breier et al. (44).

It is interesting to imagine how the personality associated with major depression or panic disorder might appear clinically. Extrapolating directly from the results of the present comparison of recovered patients and control subjects, one would imagine the prototypic person to be someone who is easily upset by events and who tends to lose objectivity at these times. He or she appears to lack social self-confidence, is introverted, and tends to depend more on others. Finally, this person shows some tendency to become dramatic or flamboyant under stress. This picture tends to agree with previous discussions in the literature (10, 12, 16).

One methodologic issue that should be considered before generalizing these findings involves our control group. This group, which had no history of psychiatric disorder, was probably healthier than the public at large. In the United States, the prevalence of lifetime history of affective disorders may run as high as 8%–9% and for panic disorder and agoraphobia as high as 5%–6% (45).

Our findings raise the questions of whether certain personality traits predict future emotional disorder, whether recovered anxiety and depressed patient groups can be distinguished by other personality mea-

asures, and whether an acute episode of emotional illness permanently alters some measures of personality from the premorbid state. These questions must be answered by future research. Clinicians should be aware that although some personality traits may be associated with the future development of emotional illness, it is not possible at this time to predict whether the illness will be anxiety or depression. Finally, on the basis of the present findings, we can conclude that depression and anxiety distort personality assessment in similar ways.

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Effects of the *Jamison-Farabee* Consent Decree: Due Process Protection for Involuntary Psychiatric Patients Treated With Psychoactive Medication

William A. Hargreaves, Ph.D., Martha Shumway, B.A., Elaine J. Knutsen, M.D.,
Anne Weinstein, M.S., and Nell Senter, Ph.D., J.D.

The Jamison-Farabee consent decree in California mandates an outside psychiatrist's review of involuntary medication of state hospital patients. Patients' rights advocates presumably hoped the decree would facilitate more frequent medication refusal, while clinicians predicted the procedure would impair patient care. Outside review led to only a 1.1% rate of medication denial; half of the patients involved deteriorated afterward. Examination of a sample of patients subject to the decree and two comparable samples 1 year and 10 years earlier suggests that patients' successful medication refusal was no more frequent after implementation of the decree and that the procedure had negligible effects on patient care or outcome for patients not denied medication.

(Am J Psychiatry 1987; 144:188-192)

Federal and state courts have repeatedly affirmed that the involuntary administration of psychotropic medication poses a threat to individual rights and liberties. When patients are a danger to themselves or to others, these rights are overridden by the state's police powers. However, the courts have consistently ruled that patients committed to involuntary treatment have at least a limited right to refuse treatment and are entitled to some form of due process protection when they are to be medicated in spite of their objection or

in the absence of their ability to give informed consent to medication. The history of this legal issue has been comprehensively reviewed by Roth (1).

The *Jamison v. Farabee* (2) consent decree in California mandates review of medication plans involving psychoactive medications (antipsychotics, antidepressants, or lithium) within 3 days of the treating physician's decision to medicate a patient. The reviews are done by independent psychiatrists who are experienced in institutional psychiatry and are not hospital employees. Reviewers approve or deny classes of prescribed medication as necessary to remedy or prevent substantial deterioration in a patient's condition. When a class of medications is denied, a patient cannot receive any drug from that class except in an emergency involving imminent danger to the patient or others. The reviewer's decision is final, although the treating physician may request re-review in response to a documented change in the patient's condition. A patients' rights advocate interviews patients before review and makes a report to the reviewer.

The plaintiffs argued that these were modest, reasonable requirements; the defendants feared treatment might be seriously disrupted. Therefore it was agreed that the procedure be implemented on a trial basis for 1 year at Napa State Hospital, starting April 1, 1984.

The procedure applies to all patients hospitalized involuntarily on temporary or permanent conservatorship and to a subset of patients admitted on 72-hour detention or 14-day certification who are considered gravely disabled but not a danger to themselves or others. Conservatees remaining in the hospital are reviewed every 90 days. Patients judged by the attending psychiatrist to be capable of informed consent and who agree to medication are excluded from review. However, during the initial implementation year, the California Department of Mental Health ordered that all conservatees be included in the review procedure, thus exempting attending psychiatrists from determining their capacity for informed consent.

In California, persons demonstrating continuing grave disability as a result of mental illness may be placed on a conservatorship for 1 year. Conservatorship is not a declaration of incompetence. The court-

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appointed conservator, usually a public agency employee, determines what mental health treatment the conservatee receives. A 30-day temporary conservatorship is typically put into effect while the court carries out a complete investigation. Persons thought to present an ongoing threat to others are not placed on a conservatorship but are detained under another statutory provision.

The right to refuse medication has been vigorously debated and remains highly controversial in both psychiatric and legal circles. Appelbaum and Hoge (3) have noted that systematic studies of the effects of procedures intended to protect the right to refuse medication have been rare. The trial implementation ordered in *Jamison v. Farabee* provided an unusual and interesting opportunity to examine its effects.

In examining the impact of the review procedures, we felt several questions seemed relevant.

Was the *Jamison-Farabee* procedure implemented as intended? If it was not, it may not provide a useful test of the impact of an outside psychiatrist's review.

Did the *Jamison-Farabee* procedure yield the benefits hoped for by patients' rights advocates? Were involuntary patients treated with less antipsychotic medication? Were patients more likely to object to medication and more likely to be successful in refusing medication? Did patients understand their rights under the decree and feel their situation was improved?

Did the *Jamison-Farabee* procedure cause adverse effects on patient care, as clinicians feared? Did a significant number of patients deteriorate or fail to improve after the reviewer denied medication? Were patients hospitalized longer than usual? Was there increased use of seclusion and physical restraint? Were patients more often involved in injury incidents? Were overall improvement rates lower after implementation of the procedure? Did hospital staff feel the procedure helped or hindered patient care?

METHOD

In examining the impact of the procedure, we relied primarily on clinical records. We focused on newly admitted patients during their first 8 weeks of hospitalization, when the effects of the procedure seemed likely, giving special attention to patients who objected to medication.

A comparison with pre-*Jamison* patients was necessary to determine whether there were changes after the *Jamison-Farabee* procedure was implemented. We selected samples of patients who were subject to the procedure and had been admitted during the first 6 months after implementation of the procedure—April through September 1984 (N=108)—and comparison samples admitted during the same months 1 year earlier (N=125) and 10 years earlier (N=183). All 416 subjects were conservatees or were on detention or certification for "grave disability" but not as a danger to themselves or others. Since nearly all patients sub-

ject to the procedure were conservatees and were never voluntary patients during their first 8 weeks in the hospital, we restricted analyses to such patients. This sample included 257 patients: 80 in 1974, 85 in 1983, and 92 in 1984.

In June 1983, medical staff at Napa State Hospital were asked for their opinions regarding the anticipated *Jamison-Farabee* procedure. In February 1985, 10 months after implementation of the procedure, medical staff were again surveyed. Thirty-one responded to the first survey, 33 (60%) to the second. In February a similar questionnaire was also completed by 210 nursing staff (approximately 27%).

Fifty-one patients in the hospital in January and February 1985, who had been seen by the *Jamison-Farabee* reviewers, were interviewed. Using a structured procedure developed through pilot interviews with similar patients, we examined their knowledge of rights that may be exercised by involuntary psychiatric patients. We also inquired about their attitudes toward antipsychotic medication, their understanding of medication refusal, and their knowledge of the *Jamison-Farabee* procedure.

We typically used analysis of variance to compare the 3 study years, dividing year effect into planned contrasts between 1974 and the mean of 1983–1984, in addition to 1983 versus 1984. Subjects were classified as medication "objectors" or "nonobjectors" according to whether any note of objection appeared in their chart during the first 8 weeks of hospitalization. The interaction of year with objector status was also examined. When we examined a variable over the first 8 weeks of hospitalization, we included the previously discussed factors as between-subjects effects, while within-subjects effects were weeks and the interactions of weeks with the between-subjects effects.

RESULTS

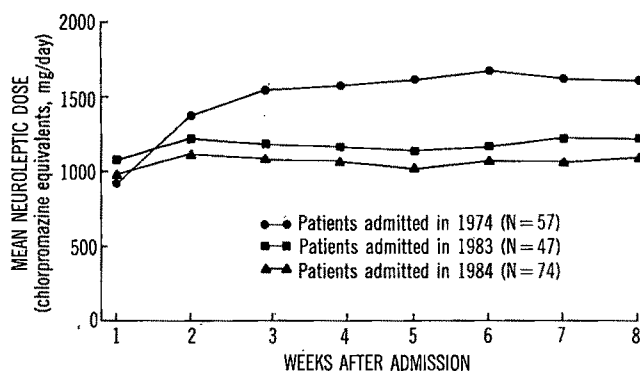
During the first year of implementation, over 2,700 reviews were performed on 1,100 patients. Analyses of data from hospital forms used in the procedures confirmed that implementation proceeded as intended (details available from the authors). The independent reviewers and hospital staff carried out the intent of the consent decree very well. Thus, any lack of effect cannot be attributed to failure in implementation.

Severity of Illness

Our samples showed increasing severity of illness due to progressive deinstitutionalization in California since 1974. One index of the change is the proportion of "*Jamison*-type" patients who were conservatees: in 1974 29% were conservatees, with the remainder on short-term involuntary holds; by 1983 70% were conservatees. In our 1984 sample only 16 were on short-term holds.

Even this restricted conservatee group showed in-

FIGURE 1. Daily Neuroleptic Doses for Patients Involuntarily Admitted to a State Hospital Before and After Implementation of the Jamison-Farabee Consent Decree of 1983



creasing severity of illness. Statistically significant trends were seen toward a greater proportion of patients who had never been married ($\chi^2=19.86$, $df=4$, $p<.001$), were receiving public assistance ($\chi^2=23.65$, $df=2$, $p<.0001$), and had shown suicidal behavior ($\chi^2=6.59$, $df=2$, $p<.04$) or aggressive, threatening behavior ($\chi^2=19.2$, $df=2$, $p<.0001$) at some time. Patients had a greater number of prior hospitalizations ($F=8.6$, $df=5, 241$, $p<.0001$) and had spent more time in psychiatric hospitals ($F=3.89$, $df=5, 248$, $p<.01$).

Medication Denial

In over 2,700 reviews there were 47 cases involving 44 patients in which the psychiatrist-reviewer denied medication. One of us (E.J.K.) performed a case-by-case analysis of these denials (unpublished manuscript). Significant deterioration occurred in 25 patients, of whom 20 were re-medicated. No adverse effects were seen in eight; the effect of medication denial was unclear for the remaining patients. Thus significant deterioration occurred in more than half of those denied medication, but the small number of denials limited the impact on the patient population as a whole. There also could have been indirect effects on patient care if the threat of review led physicians to change their prescribing practices. These effects were the main focus of our investigation.

Impact on Treatment

Patients' rights advocates presumably anticipated lower medication levels (especially in response to patient objection), more instances of successful medication refusal, and only sparing use of physical restraint.

To obtain a simple overview of antipsychotic dosing practice, we determined each subject's mean daily chlorpromazine-equivalent dose of neuroleptics for each of the initial 8 weeks of hospitalization (the methods used have been described elsewhere) (W.A. Hargreaves, M. Legouillon, R. Binder, unpublished paper). Figure 1 shows a significant decrease in mean

daily neuroleptic dose since 1974 (1974 versus 1983–1984; $F=5.98$, $df=1, 172$, $p=.02$). The small difference seen between 1983 and 1984 was not significant ($F<1$). This decrease might be partially explained by the increased use of lithium in combination with antipsychotic medication. In 1974, 88% of our subjects received only antipsychotics, while by 1983, 41% received both antipsychotics and lithium. A puzzling feature of figure 1 is that significant dose differences appeared only after 2 weeks of hospitalization (Year \times Week interaction: $F=4.28$, $df=14, 172$, $p=.001$). It appears that physicians prescribe similar dose levels at admission but in recent years have not raised the dose progressively early in hospitalization.

In all 3 years, patients who objected to medication received a lower mean dose of neuroleptics than those who did not object (main effect for objector status: $F=8.16$, $df=1, 172$, $p=.005$), but there was no indication of any change in this relationship due to implementation of the decree (Objector Status \times Year interaction: $F=1.13$, n.s.). Results for *maximum* dose were similar to those for mean dose. There was no indication that medication objectors were differentially affected by the decree, nor were whites, blacks, or other ethnic groups.

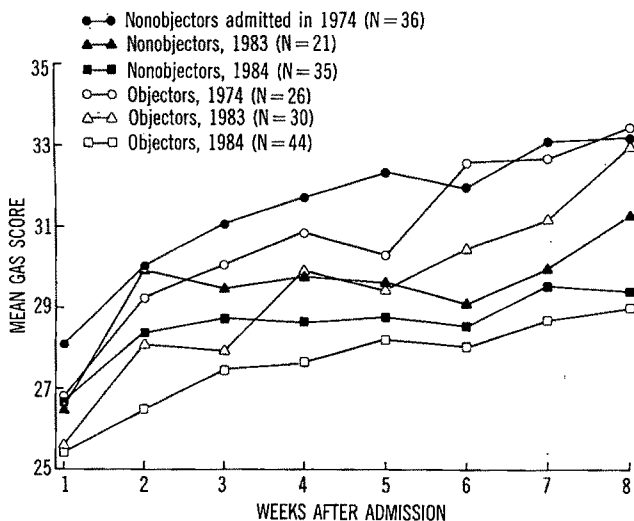
We also developed a measure of "successful" objection, noting whether there was at least 1 day during which medication was withheld in apparent response to the patient's objection. About 50% of the conservatees objected to medication at some time during their first 8 weeks in the hospital, and about 5% had at least one instance of successful medication refusal. The percentages were not significantly different over the 3 years studied. In fact, while there was a slight trend for a greater proportion of patients to object to medication in recent years, the proportion of successful refusers may even have decreased. It is possible that more severely ill patients were both more likely to object and less likely to be successful, which would explain these slight trends. There is no evidence that the *Jamison-Farabee* decree made it easier for conservatees to successfully refuse medication.

Patients and their advocates generally wish to see use of physical restraint minimized. Mean hours of physical restraint did not decrease in 1984; in fact, there was a nonsignificant trend toward an increase from 1974 to 1984. There were also no statistically significant relationships between either objector status or ethnicity and physical restraint.

Impact on Outcomes

The crudest measure of outcome is length of hospital stay. Examination of retention curves for conservatees and patients on short-term holds revealed very stable retention curves for both groups during the 8 weeks after admission. Level of functioning is a more meaningful outcome measure. On the basis of narrative notes in the clinical record, abstracters rated patients' lowest level of functioning each week using the Global

FIGURE 2. Global Assessment Scale (GAS) Scores for Patients Involuntarily Admitted to a State Hospital Who Did or Did Not Object to Medication Before and After Implementation of the *Jamison-Farabee* Consent Decree of 1983



Assessment Scale (4). Figure 2 shows similar improvement trends in all years (Year \times Week interaction: $F=1.54$, $df=14$, 1302, Huynh-Feldt $p=.14$). The overall improvement trend over weeks was highly significant, of course. More interestingly, there was a progressive decrease in level of functioning over the years (main effect for year: $F=5.06$, $df=2$, 186, $p=.01$). Medication objectors also showed more improvement over the 8 weeks in all years (Week \times Objector Status interaction: $F=2.47$, $df=7$, 1302, Huynh-Feldt $p=.04$; Week \times Objector Status \times Year interaction: $F<1$, n.s.). These results reflect yearly trends toward increasing severity of illness of the patient population and a tendency for medication objectors to be more severely ill at admission and to show greater initial improvement. However, there were no hints of any positive or negative effects of the *Jamison-Farabee* procedure on patient outcome.

The rate of injury incidents initiated by conservatees showed an increase since 1974 (1974 versus 1983–1984: $F=5.87$, $df=1$, 252, $p=.02$) but no significant change between 1983 and 1984 (1983 versus 1984: $F<1$, n.s.).

Hospital Staff Opinion

Physicians were surveyed before and after implementation of the procedure, and we found that some commonly anticipated problems were less frequent in actual practice. Most respondents said their methods for informing patients about medication had changed at least slightly. Nevertheless, their overall rating of the *Jamison-Farabee* procedure was more critical after they experienced its implementation, and their anecdotal comments were generally negative. While the decree was not seen as greatly impairing treatment, 33% thought it somewhat impaired treatment quality,

and 85% said it made their job more difficult. Nearly all asserted that the *Jamison-Farabee* decree had not affected their prescription of medication.

Nursing staff respondents gave the *Jamison-Farabee* procedure a distinctly more negative review than did physicians. The majority said it went too far in protecting the rights of involuntary patients; 25% of the respondents described it as “absurd.” Only one of 42 narrative comments was positive. Sixty percent thought the decree had caused a reduction in the typical dose of psychotropic medications, and a similar percentage thought the *Jamison-Farabee* procedure had impaired treatment quality. Almost 90% thought it made their job more difficult and that more patients had attempted to refuse medication since the decree took effect. It was clear from their comments that many felt the *Jamison-Farabee* procedure was a total waste of money that impaired treatment quality and made their work more dangerous. There is a possibility of bias in this sample, given the response rates of 60% and 27% among physicians and nursing staff, respectively, but we have no reason to think that nonrespondents would have expressed substantially different views.

Patients' Understanding of the *Jamison-Farabee* Process

Although the decree mandates uniform procedures for informing patients about medication, fewer than six of the 51 interviewed were able to list both pros and cons of medication. Only 30 of the 51 demonstrated an understanding of a simple set of patient rights. Although all of the interviewees had been reviewed, only one seemed at all aware of the *Jamison-Farabee* process.

DISCUSSION

Since trial implementation of the *Jamison-Farabee* consent decree proceeded as intended, it can be seen as an adequate test of independent psychiatrist review as a safeguard of the right to refuse medication.

The review procedure did not produce the effects hoped for by patients' rights advocates. The reviews did not reduce the average dose of antipsychotic medication received by involuntary patients, did not make it easier for patients to successfully refuse medication, and did not seem to be visible to patients as a new right or an improvement in their situation. A possible explanation for the lack of effect is that medication practices at Napa State Hospital were reasonably good when the *Jamison-Farabee* decree was implemented. In the mid-1970s public revelation of poor medication practices, an apparent series of medication-related deaths, and the 1978 filing of the *Jamison-Farabee* suit galvanized the administration and physicians at the hospital to formulate and enforce detailed medication guidelines. Our data reflect these

changes to some extent. For example, regarding the maximum number of different neuroleptic drugs used in one day at any time during the first 8 weeks in the hospital, there was a mean of 2.3 (and a range up to five) in 1974, compared to 1.1 drugs in 1983. In 1974 multiple neuroleptics were often continued for long periods, while in 1983 two neuroleptics overlapped only briefly while one was discontinued and another started. The mean number of antipsychotics received per day decreased significantly, from 1.5 in 1974 to less than one in the 2 later years (1974 versus 1983–1984: $F=71.51$, $df=1$, 229, $p<.0001$). If outside review procedures are implemented at a hospital where medication practices are poor, one might see larger effects, perhaps even a reduction in dose levels comparable to that seen at the hospital between 1974 and 1983; however, this is pure speculation on our part.

As to the right to refuse medication, our results suggest that the *Jamison-Farabee* decree is only tangentially related to the exercise of this right. Many clinicians told us they often could not judge with confidence whether a patient was “truly” refusing medication or whether a patient had the ability to give informed consent. Many instances of medication denial were clearly unrelated to patient refusal. About half of the patients objected to medication at some time during the first 8 weeks in the hospital, but only 1.1% of the reviews resulted in medication denial. Therefore the review procedure seems to offer little protection of the right to refuse medication. Roth (unpublished manuscript, 1985) has suggested that what the courts have established is a “right to a second opinion,” which seems a useful way to view the matter.

Many patients thought that if they refused medication they would be restrained and given an injection. Brief contact with the reviewer seemed to make little impression, whereas the common experience of being medicated while physically restrained probably has created a firm association between the two. Thus for these patients, it was meaningless to ask whether they thought the *Jamison-Farabee* procedure improved their lot. With rare exceptions, the procedure remained almost invisible to patients even when they themselves had been reviewed.

The disastrous effects clinicians feared did not materialize, but there were negative effects. Medication denial did seem to cause deterioration in about half of those whose medication was discontinued, but this represents less than 1% of the total cases reviewed. There is no indication that the decree had any impact on length of stay, use of seclusion and restraint, or the frequency of injury incidents. There were long-term trends toward lower levels of patient functioning and higher levels of injury incidents, which reflect the increasing severity of illness of the state hospital population. However, the rate of improvement following admission did not change after implementation of the procedure. While hospital staff, particularly nursing

staff, noted changes that have increased the difficulty and risk of their tasks, our other findings provide no confirmation that these changes should be attributed to the *Jamison-Farabee* procedure.

One clear effect of the review procedure was an increase in the cost of care. Salary costs for outside psychiatrist reviewers, the patient advocate, support staff at the hospital, and additional staff in the Department of Mental Health and nonpersonnel costs totaled over \$300,000 in the first year. This did not include clinician time preparing paperwork for reviews, a hidden cost that competes with other responsibilities. If the only concrete results were the approximately 30 instances in which medication was denied and not quickly reinstated, then each of those instances cost about \$10,000. Each of the 2,800 reviews cost over \$100, and each patient subject to the *Jamison-Farabee* procedure cost almost \$275 to process because many patients were reviewed more than once. We estimate that it will cost \$1–\$1.5 million to implement simplified procedures at the five major hospitals for the mentally disordered in California for the period 1985–1986. It has been asserted that implementation of similar procedures in other states resulted in a considerable decrease in medication costs. Since we found no change in mean antipsychotic dose after implementation of the procedure, no such savings accrued at the hospital. Whether there are offsetting savings at the other four California hospitals remains to be seen.

Do our findings indicate that outside review procedures serve no useful purpose? Not necessarily. Our expectation is that their effect will depend on two factors: the degree to which the mental health system is deinstitutionalized and the skill of hospital physicians in using psychotropic medication. If deinstitutionalization is already far along, as in California, there may be few patients in state hospitals with any usable capacity for informed consent. If there are still many hospitalized patients able to survive on the street, these procedures might trigger more discharges of patients judged capable of “informed refusal.”

Some would argue that provision of due-process safeguards on “forced drugging” is worthwhile in principle, even if practical effects cannot be demonstrated. If this remains the sole justification for a review procedure, however, perhaps a more economical approach should be devised.

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Competency Determinations in Civil Commitment

Joseph D. Bloom, M.D., and Larry R. Faulkner, M.D.

The authors present a brief overview of competency determinations in criminal justice and civil commitment proceedings and review the American Psychiatric Association's Model Commitment Statute, which gives competency a central role. They present an alternative proposal that involves determining a person's competency to undergo civil commitment before a formal commitment hearing and delineates the responsibilities of legal and medical decision makers in the commitment process.

(Am J Psychiatry 1987; 144:193-196)

The controversy surrounding the legal doctrine of the right to refuse treatment has refocused psychiatry on the issue of competency determinations within the civil commitment system. Modern commitment statutes separate civil commitment from civil competency. In this separation between commitment and competency the right to refuse treatment was born, and it continues to thrive (1). In a previous paper on the right to refuse treatment (2) we discussed three models that deal with patients who refuse treatment. The clearest response to the dilemma was enacted in Utah, where a specific finding of incompetency to make treatment decisions was placed in the commitment standard (3). Two other contrasting responses, one emphasizing medical and the other legal decision making, have received intense scrutiny. The legal decision-making model developed in Massachusetts (4) requires that any civilly committed patient who refuses treatment be returned to court for a competency

hearing before treatment is initiated in a nonemergency situation. The model favoring medical decision making, developed in New Jersey, initially required a review of the refusing patient by an independent psychiatrist. This model has recently been changed to permit internal hospital review of the treatment refusal (5). These medical and legal models for reviewing treatment refusal share a concern for the competency of the individual but take opposite approaches to making decisions for mentally ill persons.

In this paper we present a brief overview of the current status of competency in both criminal justice and civil commitment proceedings, contrasting the roles of lawyers and psychiatrists in each process. We review the Model Commitment Statute proposed by APA (6), emphasizing the importance it gives to the issue of competency. We then propose an alternative model for fitting competency determinations into the civil commitment process and conclude with a discussion of the major implications of our proposal.

CRIMINAL JUSTICE AND CIVIL COMMITMENT PROCEEDINGS

To clarify some of the issues pertaining to competency in civil commitment, it is helpful to contrast competency determinations in the criminal justice and civil commitment systems. In the criminal justice system, the defense attorney, prosecutor, and judge should raise the question of a defendant's competency whenever they believe the defendant may not be able to participate adequately in his or her trial. Competency determinations may occur at any stage in the pretrial, trial, and sentencing phases of a criminal prosecution. The legal criteria for competency include the ability to understand the nature of the judicial proceedings and to consult rationally with a lawyer in order to prepare a defense (7). Legal tradition has dictated that a defendant should be competent to help guarantee the fairness and accuracy of criminal pro-

Received Dec. 23, 1985; revised June 19, 1986; accepted Aug. 11, 1986. From the Law and Public Policy Section, Community Psychiatry Training Program, Department of Psychiatry, Oregon Health Sciences University. Address reprint requests to Dr. Bloom, Department of Psychiatry, Oregon Health Sciences University, 3181 S.W. Sam Jackson Park Rd., Portland, OR 97201.

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ceedings, the efficacy of punishment, and the dignity of the judicial process. Once the issue of competency is raised, the defendant is usually examined by a psychiatrist, and the judge makes the final competency decision. Legal and medical responsibilities and roles are well circumscribed in the criminal justice process.

In the civil commitment system we see an entirely different situation. In modern civil commitment statutes, a person who is allegedly mentally ill is involved in a series of legal procedures and hearings every bit as complex and confusing as those in the criminal justice system (8). However, the person is presumed to be competent to understand the nature of the proceedings and to assist his or her attorney. Although an individual has a right to an attorney, there is no process available for questioning whether a person is able to participate meaningfully in the commitment process. The rush to replace "medical paternalism" in the civil commitment process with specific substantive criteria and procedural safeguards (9) may have gone too far. What value is a carefully constructed legal process to a participant who might be incompetent to understand the nature of the legal process or to cooperate in any meaningful way with his or her attorney?

What can be said about the roles of attorneys and psychiatrists in civil commitment? It appears that many lawyers are in a quandary about their role in civil commitment proceedings when they represent individuals who are obviously very disturbed and medically in need of treatment (10-12). Although some attorneys always take an adversarial stance, the majority apparently do not (13). Instead, they either acquiesce to the opinions expressed by the psychiatrists who have examined their clients or vary their advocacy efforts depending on their own assessments of what is best for their clients. Given the inescapable conclusion that many individuals involved in civil commitment proceedings are incompetent to make decisions about their care and treatment (14), attorneys who always advocate release are, in fact, frequently pursuing their own course of action under the guise of following the stated wishes of their clients. On the opposite pole, attorneys who always heed the advice of the psychiatrists almost never follow the stated wishes of their clients. They help perpetuate what has been described as a "legal charade" (15) and an "empty ritual" (16). Whatever role is chosen by a given attorney, it is very important because it has been shown to exert a significant influence on the outcome of civil commitment proceedings (17).

The role of psychiatrists in civil commitment proceedings is equally confusing. Originally, most civil commitment statutes merely required psychiatrists to determine whether they believed a person was mentally ill and in need of treatment. Modern commitment statutes, however, demand that psychiatrists determine not only whether a person has a mental disorder but also whether he or she is dangerous (8). Although psychiatrists are capable of expressing informed opinions about the existence of a mental disorder, they

have no special expertise concerning the prediction of dangerousness (18).

Modern commitment statutes have actually done little to correct the theoretical biases of older procedures. Instead of psychiatrists deciding what is best for people and who should be treated, we now have attorneys doing essentially the same things. "Medical paternalism" has been replaced by "legal paternalism" (11). In addition, although psychiatrists no longer determine who will be committed, they still exert a strong influence over the process with their predictions concerning a person's potential for dangerousness. Modern commitment proceedings, therefore, suffer from the worst of both worlds: uninformed legal decision making concerning medical issues and uninformed medical decision making concerning legal issues.

MODEL COMMITMENT STATUTE

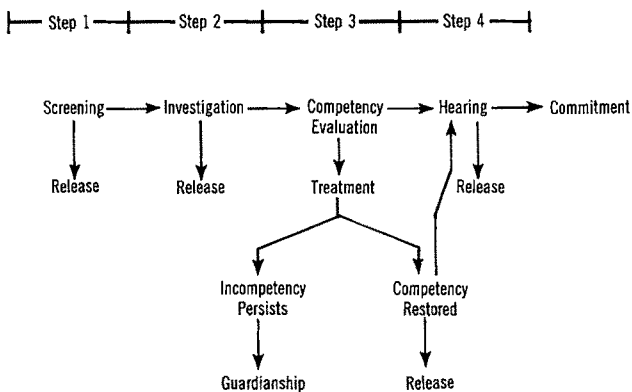
The Model Commitment Statute of APA (6), an adaptation of work done earlier by Stone (19) and Roth (20), places a competency determination in a central position within the standard. The specific criteria for commitment (6) are as follows:

1. The person is suffering from a severe mental disorder; and
2. there is a reasonable prospect that his disorder is treatable at or through the facility to which he is to be committed and such commitment would be consistent with the least restrictive alternative principle; and
3. the person either refuses or is unable to consent to voluntary admission for treatment; and
4. the person *lacks capacity to make an informed decision concerning treatment* [emphasis added]; and
5. as the result of the severe mental disorder, the person is a) likely to cause harm to himself or to suffer substantial mental or physical deterioration, or b) likely to cause harm to others.

The APA model statute (6) defines the lack of capacity to make an informed decision as follows:

Lacks capacity to make an informed decision concerning treatment means that the person, by reason of his mental disorder or condition, is unable, despite conscientious efforts at explanation, to understand basically the nature and effects of hospitalization or treatment or is unable to engage in a rational decision-making process regarding such hospitalization or treatment, as evidenced by inability to weigh the possible risks and benefits.

Although it is an improvement over usual commitment statutes, from our perspective the APA statute still has problems in relation to both psychiatrists and attorneys. APA's model statute continues to require that psychiatrists make a prediction of dangerousness, and although individuals are guaranteed legal counsel, attorneys are still given no role in ensuring that their

FIGURE 1. Proposed Civil Commitment Process

clients can understand what is happening to them. Attorneys are left to follow their own inclinations with respect to the vigor of their advocacy efforts.

COMPETENCY TO STAND TRIAL FOR CIVIL COMMITMENT

We have previously proposed a model that divides civil commitment processes into separate steps at which specific decisions must be made (21). This model is applicable to most state statutes. The typical commitment process consists of steps 1, 2, and 4 in figure 1. In step 1 (screening) the decision is whether a person should formally enter the civil commitment process. In step 2 (investigation) the decision concerns the certainty with which it can be shown that the person is mentally ill as defined by law and therefore fulfills acceptable criteria for a commitment hearing. If so, a hearing is scheduled. In step 4 (hearing) the decision is once again whether the person is mentally ill, with a more stringent burden of proof.

Step 3 in the figure is our proposed addition to the civil commitment process. It consists of a competency evaluation performed after the investigation and before the commitment hearing. Before a competency evaluation, therefore, probable cause of mental illness is established, and the person involved in the commitment process is assigned an attorney. The major decision at this step is whether the person is competent to stand trial for civil commitment. Does he or she understand the nature of the civil commitment proceedings, and can he or she assist the attorney in preparing a defense? If the defense attorney believes there is doubt concerning the client's ability to understand or participate in the proceedings, he or she should make this concern known to the judge, who may then order a formal competency evaluation. Similarly, if the judge or prosecuting attorney doubts the person's competency, he or she may also raise the question. On the basis of the evaluation, the judge may either decide that the person is competent and proceed with a hearing or refer the person for treatment in an

effort to restore competency. If the person remains incompetent after a specific period of treatment, then guardianship should be arranged. Whenever the person's competency to stand trial for civil commitment has been restored, the judge may, on recommendation of the treating facility, decide either to release him or her or to proceed with a commitment hearing (step 4).

DISCUSSION

There are several implications of our proposal that merit discussion. First, like the Utah (3) and the APA (6) statutes, this proposal addresses the issue of competency within the civil commitment process before a formal commitment. Unlike the Utah and APA statutes, however, our proposal initially changes the focus of that competency determination from the ability of a person to make an informed treatment decision to the ability of a person to understand the commitment process itself. Conceptually, it seems to us that this ought to be the first competency issue to resolve. This proposal helps to clarify some of the roles and responsibilities of key decision makers in the commitment process. Attorneys and judges have the responsibility to ensure that persons involved in the legal process of civil commitment are competent to understand and take part in it. Attorneys are not expected to try to figure out what is best for their clients.

Second, this proposal is compatible with current commitment statutes. By raising the question of competency after it has been established that a probable cause of "mental illness" exists, only those people already involved in the commitment process would be eligible for competency evaluations. This proposal could not be used to divert additional numbers of people into the mental health system. Since competency to stand trial for civil commitment would be established before the formal commitment hearing, current hearing procedures and commitment criteria could continue as they are now.

Third, this proposal would create a new group of hospitalized persons who are incompetent to stand trial for civil commitment and would also increase the number of persons under guardianship. This raises the specter of potential abuse. We contend that this is a step forward for those people truly incompetent to stand trial for civil commitment. It makes no sense whatsoever to involve them in legal proceedings that they do not understand. To do so is merely a sham effort to make it appear that their rights are being preserved. The potential for abuse of these procedures could be minimized by applying standards that specify the criteria for incompetency to stand trial in civil commitment, the length of hospital treatment permissible to restore competency, the length of guardianship permissible, and the frequency of required competency reevaluations.

In summary, we believe our proposal has substantial advantages because it helps to establish that people

understand what is happening to them as they proceed through the civil commitment process. If we are going to have a legally oriented civil commitment process, then let us at least have one that is fair and meaningful to the people involved.

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Predictive Validity of Judgments of Dangerousness in Emergency Civil Commitment

Dale E. McNiel, Ph.D., and Renée L. Binder, M.D.

The authors investigated the predictive validity of judgments of dangerousness made in the context of emergency civil commitment. The medical charts of 101 consecutive patients involuntarily admitted to a university-based acute inpatient unit were reviewed for evidence of violence within the first 72 hours of hospitalization. More than two-thirds of the patients committed as a danger to others engaged in some type of violence, compared with fewer than one-third of other involuntary patients. The findings suggest that the emergency commitment situation permits judgments of dangerousness with a relatively high degree of short-term predictive validity.

(Am J Psychiatry 1987; 144:197-200)

Although dangerousness is a criterion for civil commitment in virtually every state (1), empirical support for the accuracy of clinical predictions of violent behavior in psychiatric patients is sparse (2). The lack of evidence for clinicians' ability to accurately predict violence has been cited to support arguments for abandonment of dangerousness as a basis for civil commitment (3-5). Previous studies of psychiatric predictions of violence (6, 7), however, have generally examined long-term predictions of the behavior of institutionalized patients after discharge. This situation is quite different from the predictions of imminent dangerousness made at the point of a patient's entry

into the civil commitment process, i.e., in the context of emergency civil commitment. Monahan (8, 9) has suggested that the emergency civil commitment situation may permit relatively valid predictions of violence, in part because of the small temporal gap between the behavior used as a predictor and the outcome being predicted.

One way to assess the validity of judgments of dangerousness in the emergency civil commitment situation is to determine whether patients involuntarily hospitalized on the basis of dangerousness engage in more violent behavior during the commitment than other patients. Two studies (10, 11) have reported the incidence of violent behavior after the emergency commitment of male patients to Veterans Administration hospitals. However, the design of these studies militated against accurate assessment of the validity of the judgments of imminent dangerousness that were the basis of the emergency commitments. In both studies, the follow-up periods were much longer than the emergency commitments.

The purpose of this study was to determine whether patients involuntarily committed because they were judged to be a danger to others were more likely to engage in violent behavior within the first 72 hours of hospitalization than involuntary patients who were not judged to be a danger to others. To our knowledge, this is the first study to assess the validity of judgments of dangerousness in the emergency civil commitment situation over a short follow-up period. In addition, this is the first study to investigate this issue on an acute inpatient unit serving a heterogeneous community mental health center population.

METHOD

The subjects included all patients admitted involuntarily during the first 6 months of 1984 to a university-based locked short-term treatment unit that provides

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TABLE 1. Proportion of Patients With Assault-Related Events During 72-Hour Involuntary Holds for 48 Patients Judged Dangerous to Others and 56 Patients Not Judged Dangerous to Others

Event	First 24 Hours				Second 24 Hours				Third 24 Hours				Entire 72-Hour Hold			
	Judged Dangerous		Not Judged Dangerous		Judged Dangerous		Not Judged Dangerous		Judged Dangerous		Not Judged Dangerous		Judged Dangerous		Not Judged Dangerous	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Physical assault	11	23	3	6 ^a	3	6	1	2	2	4	1	2	13	28	4	7 ^a
Seclusion for dangerousness	18	38	5	9 ^b	8	17	2	4	3	6	1	2	23	49	6	11 ^c
Four-point restraints for dangerousness	8	17	1	2 ^a	1	2	1	2	2	4	0	0	9	19	1	2 ^b
Verbal assaults	28	60	14	26 ^b	27	57	13	24 ^b	10	21	5	9	33	70	16	30 ^c
Any event	30	64	14	26 ^b	27	57	13	24 ^b	11	23	5	9	34	72	16	30 ^c

^aSignificant difference between groups ($p < .05$).^bSignificant difference between groups ($p < .01$).^cSignificant difference between groups ($p < .001$).

inpatient psychiatric services for a largely middle-class urban catchment area of approximately 200,000. The medical record of each patient was reviewed by one of us (D.E.M.) to determine legal status at admission and evidence of violent behavior on the ward.

Legal status at admission was based on the Lanterman-Petris-Short Act of 1969. This statute provides for the commitment of mentally ill patients for up to 72 hours on the basis of a judgment by an authorized mental health professional or a peace officer that the patient is a danger to others, a danger to self, and/or gravely disabled (California Welfare and Institutions Code, Section 5150). In making the decision whether or not to commit a patient, the clinician takes into account all the relevant information available at the time.

For the purposes of this study, legal status was categorized as "a danger to others" or "not a danger to others." A patient was rated as a danger to others if he or she had been placed on a 72-hour involuntary hold on the grounds of danger to others, regardless of whether the additional grounds of danger to self and grave disability had been applied. A patient was rated as not a danger to others if he or she had been placed on a 72-hour involuntary hold on the basis of danger to self and/or grave disability.

During the 6 months of the study, 101 patients were admitted on 72-hour involuntary holds, 47 patients were admitted as a danger to others, and 54 patients were committed on grounds other than danger to others. Forty-eight percent were women and 52% were men. The mean \pm SD age was 39.2 ± 13.8 years (range = 19–92 years). Fifty-four percent were Caucasian, 20% were Asian, 14% were black, and 12% were of other ethnic backgrounds. Ninety-three percent were in the lowest two social classes (Hollingshead's class IV or V). The sample included these diagnostic groups according to ICD-9-CM: schizophrenic disorders (36%), affective psychoses (34%), and other mental disorders (30%).

Violent behavior was rated on the basis of progress notes and other routine forms on which ward staff are

required to record all such incidents each shift. We used a modified version of an unpublished ward behavior checklist developed by John Lion, M.D. (personal communication, 1985) for determining whether or not each of the following assault-related events occurred during each of the 3 days after a patient was placed on a 72-hour hold: 1) physical assault against others, 2) seclusion as a result of being dangerous to others, 3) use of four-point restraints as a result of being dangerous to others, and 4) verbal assault against others, i.e., threats to physically harm others or pointedly abusive and hostile verbal behavior.

RESULTS

Comparison of the patients judged to be a danger to others and those not judged to be a danger to others revealed no significant differences on any of the demographic variables, except that men were more likely than women to be admitted on the basis of danger to others ($\chi^2 = 7.46$, $df = 1$, $p < .01$).

Chi-square analyses, corrected for continuity, were used to evaluate whether legal status was associated with the occurrence of the assault-related events on the ward behavior checklist. We evaluated this in two ways: first, we assessed whether legal status was associated with the patients having any days during the entire 72-hour hold on which they had an assault-related event. Next, we evaluated the association between legal status and the presence or absence of assault-related events considering each day of the 72-hour hold separately.

The numbers of patients who engaged in assault-related events are shown in table 1. During the entire 72-hour hold, over two-thirds of the patients judged to be dangerous engaged in at least one assault-related event, compared to fewer than one-third of the patients not judged to be dangerous ($\chi^2 = 16.7$, $df = 1$, $p < .0001$). The same pattern was evident when each category in the ward behavior checklist was considered separately. A significantly greater proportion of the

patients judged to be dangerous engaged in each of the four categories of assault-related events during the entire 72-hour hold.

Examination of each of the 3 days of the 72-hour hold separately suggests that the differences between the patients judged to be dangerous and those not judged to be dangerous were related to length of time in the hospital. During the first day after admission, the group judged to be dangerous included significantly more patients who were physically assaultive ($\chi^2=5.3$, $df=1$, $p<.05$), were verbally assaultive ($\chi^2=10.4$, $df=1$, $p<.01$), required seclusion ($\chi^2=10.4$, $df=1$, $p<.01$), and required restraints ($\chi^2=5.4$, $df=1$, $p<.05$). On the second day of hospitalization, significantly more of the patients judged to be dangerous were verbally assaultive ($\chi^2=10.3$, $df=1$, $p<.01$), and there was a nonsignificant trend for more of them to be secluded ($\chi^2=3.6$, $df=1$, $p<.06$), but the difference in the proportion of patients in the two groups who were physically assaultive or were placed in four-point restraints was not significant. By the third day of the 72-hour hold, there was no significant association between legal status and any of the four types of assault-related events on the ward behavior checklist.

DISCUSSION

Our findings support the predictive validity of clinical judgments of dangerousness made in the context of emergency civil commitment. Specifically, patients hospitalized on the basis of a judgment that they represented a danger to others engaged in more violent behavior in the first 72 hours of hospitalization than involuntary patients not judged to be dangerous. This difference was both statistically and clinically significant. However, emergency commitment based on danger to others predicted inpatient violence only in the short term. Although patients committed as dangerous were more likely to be violent on the first day of hospitalization, by the third day after commitment the proportion of violent patients was no higher in the group committed as dangerous to others than in the control group. One plausible explanation for this is that by the third day of hospitalization, clinical interventions such as psychotropic medications and ward structure had decreased the patients' violence potential, so that neither group of patients engaged in much violent behavior.

Two of three patients who were committed on the basis of danger to others engaged in some type of violent behavior within the first 3 days of hospitalization. The extent to which the judgments of dangerousness accurately predicted violence in the hospital is remarkable in view of the large differences between the hospital setting and the community setting in which the behavior occurred that led to the involuntary commitment. One might expect that the patients judged to be dangerous would have been even more violent if they had not been committed to the struc-

tured treatment setting but had instead returned to the community.

To our knowledge, this study is the first to investigate the predictive validity of judgments of dangerousness in the emergency civil commitment situation using a heterogeneous community mental health center patient population. The two previous studies that addressed this issue used male veterans as subjects (10, 11). Rofman et al. (10) also found that patients committed as dangerous were more violent than control subjects, but their study is not directly comparable to ours because voluntary patients were used as a control group, whereas our study used involuntary patients not judged to be a danger to others as control subjects. However, Yesavage et al. (11) found no difference in the rate of violence between patients committed as a danger to others and other involuntary patients. Aside from differences in the patients studied, two major factors could account for the discrepancy between our findings and those of Yesavage et al. First, Yesavage et al. used a follow-up period of 7 days, whereas we used a 3-day follow-up period. As already discussed, the short-term follow-up period is more relevant for evaluating the predictive validity of emergency civil commitment, in which the assessments made are regarding *imminent* dangerousness. A second factor is that the civil commitment statute may have been applied differently in the two studies. Previous research suggests that community practices regarding the application of civil commitment statutes can vary in different regions (12) and at different times in the same region (13).

Our findings have implications for the continuing controversy regarding the appropriateness of dangerousness as a criterion for emergency civil commitment. Some (3–5) have argued that the dangerousness standard should be abolished because psychiatric predictions of dangerousness are inaccurate. However, the studies cited by critics of the dangerousness standard only demonstrate the inaccuracy of long-range psychiatric predictions of the dangerousness of institutionalized patients after discharge. Those data are not directly relevant to the emergency civil commitment situation. The results of the present study suggest that emergency commitment based on dangerousness does serve to protect society, in that a large percentage of patients judged to be dangerous did become violent in the hospital. Furthermore, our findings suggest that the rate of false-positive predictions of dangerousness is not as high in the emergency commitment setting as it may be in other settings. Although many complex issues are involved in developing policy regarding civil commitment (14, 15), our data warrant consideration when comparisons are made between the relative costs (e.g., loss of liberty) and benefits (e.g., protection of the community from harm) of emergency civil commitment based on dangerousness.

In conclusion, although clinical predictions of violence may be inaccurate in many settings, the results of this study suggest that the emergency civil commitment

situation permits judgments of dangerousness that have a relatively high level of predictive validity in the short term.

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Sleep Reduction as a Final Common Pathway in the Genesis of Mania

Thomas A. Wehr, M.D., David A. Sack, M.D., and Norman E. Rosenthal, M.D.

Diverse psychological, interpersonal, environmental, and pharmacological factors that appear to trigger the onset of mania could act via their capacity to cause sleep deprivation, a mechanism that has been shown in experiments with bipolar patients to induce transient or sustained switches into mania. Since mania in turn causes insomnia, the development of mania is potentially self-reinforcing and could become autonomous after being initiated by precipitating factors. The sleep reduction model is based on experimental evidence and is a parsimonious explanation for the precipitation of manic episodes by a wide variety of factors. Furthermore, this model has clear implications for the prevention and treatment of mania and provides a conceptual focus and an experimental paradigm for psychological investigations of the causes of mania.

(Am J Psychiatry 1987; 144:201-204)

Frequently . . . insanity originates indirectly . . . from the psychical causes A mediator . . . of especial importance and frequency in connection with mental diseases is continued sleeplessness, which often accompanies the depressing emotions, which overexcites the brain It presents, therefore, in the preliminary stages of insanity, a symptom which may be often effectually combatted by therapeutic measures.

Wilhelm Griesinger
Mental Pathology and Therapeutics (1985)

A variety of factors have been implicated as causes of manic episodes. These include external events, such as disruptions in routine due to job change, travel, or moving (1-7), and stressful or emotionally charged experiences connected with interpersonal relationships, such as infatuation, separation, and loss (1, 3-5, 8-18). The incidence of mania increases during the postpartum period (19), when many environmental, psychological, interpersonal, and hormonal changes occur. Administration (20, 21) and withdrawal (22-24) of various drugs and hormones have

also been implicated as causes of mania. The validity of the concept of precipitating factors has been questioned by some investigators (25, 26), but the issue of validity is beyond the scope of this paper.

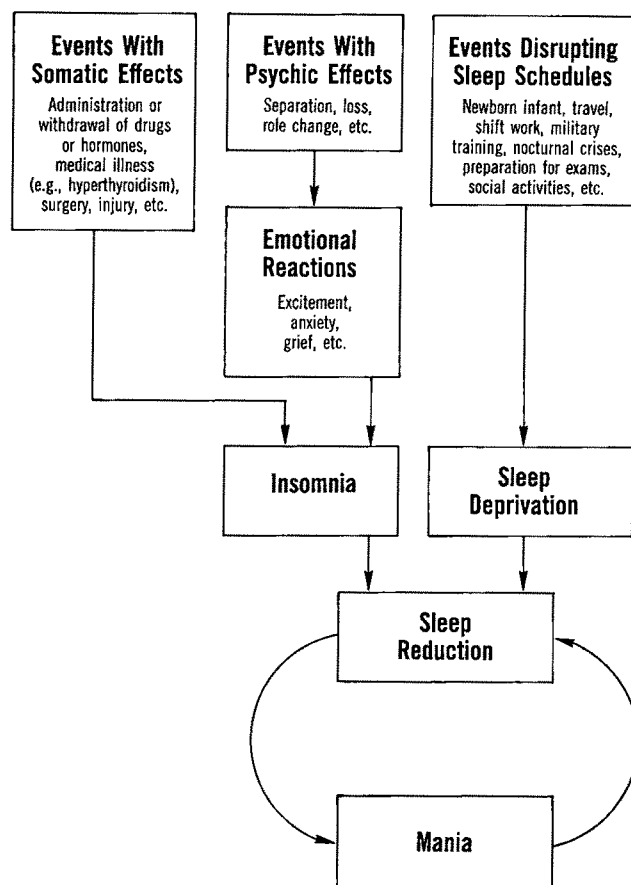
Many of the factors believed to play a role in inducing mania interfere with sleep. Disruptions of routine connected with travel or various types of emergencies may preclude sleep. Emotional reactions to people and events, such as excitement, anxiety, fear, grief, and despair, commonly cause insomnia. Sleep is often disrupted in the postpartum period by the demands of feeding and caring for a newborn infant. Drugs, such as amphetamines and monoamine oxidase inhibitors, and hormones, such as thyroxine, reduce sleep. Sleep is also disrupted during withdrawal from alcohol and from various drugs used to treat bipolar patients, including antidepressants, neuroleptics, lithium, minor tranquilizers, and sedatives (23, 27).

We propose that many of the diverse psychological, interpersonal, environmental, and pharmacological factors that appear to trigger the onset of mania could do so through their capacity to cause sleep deprivation. In experiments in which sleep has been manipulated as an independent variable, partial or total sleep deprivation for one night has been shown to induce transient or sustained switches into mania or hypomania in bipolar patients. For example, using methods and subjects described elsewhere (28), we deprived 12 depressed bipolar patients of sleep for one night; nine (75%) switched into mania or hypomania during that night or the following day, three switched back into depression after recovery sleep, and six remained manic for days or weeks. Others (29-36) have also reported that sleep deprivation can induce mania.

Although sleep reduction causes mania, mania also causes sleep reduction. In fact, the onset of mania is sometimes accompanied by alternate nights of total insomnia (28). The results of the sleep deprivation experiments strongly suggest that the insomnia caused by mania in turn exacerbates or sustains the mania. Thus, the causal relationship between sleep loss and mania is bidirectional and results in a vicious circle that could spiral out of control because of its self-reinforcing properties. In this way, sleep loss arising from a variety of causes could set in motion a manic process that is capable of becoming autonomous (see figure 1). Because of the clear experimental evidence that sleep deprivation induces mania, it seems reason-

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FIGURE 1. Diagram of Hypothesis of Sleep Reduction as Final Common Pathway of Diverse Factors Thought to Precipitate Mania



able to postulate that factors which both interfere with sleep and appear to induce mania do so through the mechanism of sleep deprivation. The postulated relationship of precipitating events, sleep loss, and mania is illustrated by the following examples.

CASE REPORTS

Case 1. Dr. A, a 25-year-old bipolar patient on maintenance lithium carbonate treatment, had been mildly depressed during his last year of medical school. During the first 2 months of his internship, he was on call at the hospital every third night. When on call, he was unable to obtain more than a few hours of sleep during the night. Each day after the on-call night Dr. A became hypomanic; he became euthymic on the second day and mildly depressed on the third. Thus, he developed a rapid-cycling course of manic-depressive illness that was driven by external factors regulating his sleep schedule. Because of his hypomanic behavior, he was encouraged by supervisors to seek a consultation regarding the management of his illness. He responded to an increase in the dose of lithium carbonate, which attenuated the severity of his hypomania.

Case 2. For the past 2 years Mr. B, a 28-year-old bipolar patient, drove 800 miles to spend the Christmas holidays with his family. Impatient to return home and unable to find

a motel room, he drove through the night without stopping until he reached his parents' house. By the time of his arrival, Mr. B, who had been euthymic, became hypomanic. The first year the mania escalated and required his hospitalization; the following year it was possible to attenuate the severity of his mania through early treatment with adjunctive neuroleptic medications.

Case 3. Mr. C, a 20-year-old college student, became romantically involved with a girl from a college in a neighboring city. She invited him to visit her in her home town during spring vacation. After pleasurable anticipation of the visit, he arrived and discovered that she had become interested in someone else and did not wish to see him. Lonely and dejected, he passed a sleepless night in an unfamiliar hotel. The following day he began to exhibit signs and symptoms of his first manic episode. He failed to return to college and began to engage in a variety of bizarre activities. Ultimately, he was arrested for operating an illegal radio station, was hospitalized, and responded to lithium carbonate.

Case 4. Ms. D, a 50-year-old woman who had been depressed for several months, took an overnight transatlantic flight from the United States to Europe to visit her family. Like many passengers, she slept very little (if at all) during the flight and by the time of her arrival the following morning had switched into her first hypomanic episode. The hypomania continued unabated for several weeks and did not require treatment. Ultimately, she relapsed into depression. Maintenance treatment with lithium carbonate failed to prevent depressive relapses. Having inferred that her switch into hypomania resulted from sleep deprivation, she periodically used it successfully to treat her recurrent depression.

DISCUSSION

In each case, the onset of mania immediately followed external events that induced sleep deprivation directly through interference with sleep schedules or indirectly through emotional responses that disturbed sleep. Although the switches into mania could be attributed to factors other than sleep deprivation, such alternative explanations may be unnecessary in light of the known capacity of sleep deprivation to induce mania. This model does not exclude interpersonal and psychological factors as causes of mania; rather, it provides a plausible mechanism and a final common pathway through which such factors could operate. According to the model, interpersonal and psychological factors are causative when they disrupt sleep (e.g., insomnia caused by grief giving rise to bereavement manias [16]); they may not be causative when they occur in conjunction with sleep loss due to other factors (e.g., sleep loss secondary to changes in routine or travel). Depending on one's training and point of view, one might be inclined to attribute the onset of mania in the case of the all-night driver (case 2) to psychological factors related to his reunion with his family or to an anniversary reaction connected with the holiday season. Sleep deprivation incurred in traveling is a more prosaic explanation, but it is a sufficient

one. The hypothesis of a sleep deprivation mechanism for travel-related mania fits very well the observations of Jauhar and Weller (7), who found an association of west to east (i.e., overnight) flights with hospitalizations for mania among patients from Heathrow airport.

It could be argued that insomnia associated with depression should precipitate mania in bipolar patients. In fact, as many as half of all manic episodes are preceded by depressive episodes (37). In some bipolar patients with decreased sleep during depression, the degree of sleep reduction may be insufficient to induce a switch out of depression into mania; our experiments with partial sleep deprivation suggest that sleep must be reduced to less than 4 hours to elicit a change in clinical state (unpublished data of Sack et al.). On the other hand, many bipolar patients are hypersomnic when depressed (38) and thus are not subject to the effects of sleep reduction.

In experiments with patients, recovery sleep sometimes reverses switches into mania that were induced by sleep deprivation (28). In a similar way, manias induced by sleep loss in the clinical setting sometimes might be short-lived. In these instances, we presume that the level of activation induced by sleep loss on one night produces too little insomnia on the following night to become self-reinforcing.

How does sleep deprivation cause mania? In proposing sleep reduction as a final common pathway for induction of mania in diverse situations, we are not specifying the mechanism through which sleep deprivation exerts its effects. We have previously hypothesized (39) that depression is a sleep-dependent process and that depression might occur when a sleep-sensitive, circadian phase interval normally associated with the first hours of wakefulness is abnormally advanced into the last hours of sleep and interacts with sleep to produce depression. The sleep reduction model is compatible with the phase advance hypothesis in that sleep reduction would be predicted to promote switches out of depression into mania by interfering with the hypothesized interaction of sleep with a sleep-sensitive circadian phase interval. However, the sleep reduction model leaves open other possible mechanisms.

To date, the most dramatic biochemical correlates of sleep deprivation have been found in neuroendocrine systems. Sleep deprivation stimulates thyrotropin (TSH) (40) and cortisol (41) secretion and inhibits prolactin (42) and growth hormone (43) secretion. Sleep deprivation has little effect on plasma metabolites of neurotransmitters such as norepinephrine and dopamine (unpublished data of Sack et al.). In light of evidence that thyroxine or hyperthyroidism can cause mania (44), stimulation of the thyroid axis deserves further investigation as a possible mechanism through which sleep reduction induces switches into mania. The fact that sleep reduction stimulates the thyroid axis and stimulation of the thyroid axis induces sleep reduction indicates that this axis could participate in

the vicious circle of sleep reduction and mania. The importance of disruption of REM sleep in patients' responses to sleep deprivation also needs to be considered, since selective REM sleep deprivation has been shown to have antidepressant effects (45).

TREATMENT IMPLICATIONS

The hypothesis that disruption of sleep is the mechanism through which many factors cause mania in the natural course of the illness was suggested, and is supported, by experiments that show that sleep deprivation induces mania. It provides an inclusive explanation of how diverse psychological, social, environmental, and biological factors may precipitate manic episodes. Moreover, the capacity of reductions in sleep to cause mania and of mania, conversely, to reduce sleep constitutes a self-reinforcing mechanism that, in turn, could explain the tendency of mania to escalate out of control and become autonomous.

The knowledge that sleep reduction can cause mania may be used by patients, their families, and the persons who care for them to help prevent and to alleviate mania. A single night of sleep loss in a bipolar patient could be useful as an early warning of possible impending mania. The risk of mania might be reduced by eliminating or mitigating factors that interfere with sleep. Patients at risk for mania could be counseled to avoid situations likely to disrupt sleep. Psychological management of emotional crises that can disturb sleep could be provided. Drugs known to interfere with sleep could be avoided. Care could be taken to avoid insomnia resulting from rapid withdrawal of drugs, such as antidepressants. Pharmacological treatment of insomnia could be expected to prevent or attenuate manic episodes, as has been reported to occur with the sedative drug clonazepam (46).

Knowledge that sleep reduction can precipitate mania would also provide a conceptual focus and an experimental paradigm (sleep deprivation) for psychological investigations of the causes of mania.

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Prevalence of Tobacco Dependence and Withdrawal

John R. Hughes, M.D., Steven W. Gust, Ph.D., and Terry F. Pechacek, Ph.D.

In a sample of 1,006 middle-aged male smokers drawn from the general population, 90% (N=905) fulfilled DSM-III criteria and 36% (N=362) fulfilled Fagerstrom's criteria for tobacco dependence. Among the 875 who had stopped smoking in the past for at least 24 hours, 21% (N=184) fulfilled DSM-III criteria and 46% (N=403) fulfilled the authors' own criteria for tobacco withdrawal. Concordance of results among the criteria for diagnosing tobacco dependence and withdrawal was low. These results suggest that the DSM-III criteria for tobacco dependence are overinclusive and that there is little consensus among the definitions of tobacco dependence and withdrawal.

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Researchers in the National Institute of Mental Health's Epidemiologic Catchment Area Program reported that the 6-month prevalence of drug dependence in the United States is less than 10% (1, 2). However, this survey omitted two common substance use disorders: tobacco dependence and tobacco withdrawal. Tobacco dependence is defined by *DSM-III* (pp. 176-178) as 1) continuous use of tobacco for at least 1 month plus 2) either unsuccessful attempts to abstain, development of tobacco withdrawal symptoms, or continued use of tobacco despite having a tobacco-induced illness. Tobacco withdrawal is defined by *DSM-III* (pp. 159-160) as use of more than 10 cigarettes per day that contain at least 0.5 mg of nicotine and occurrence of at least four of the following within 24 hours of stopping smoking: craving for tobacco, irritability, anxiety, difficulty concentrating, restlessness, headache, drowsiness, and gastrointestinal disturbances.

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Thirty-three percent of Americans smoke (3). The proportion of these smokers who are tobacco dependent or experience withdrawal is virtually unknown (4). The few previous studies of the prevalence of tobacco dependence and withdrawal used select populations (e.g., patients in smoking-cessation clinics) and unvalidated criteria (5); thus, the generalizability and validity of their results can be questioned.

Knowledge of the prevalence of tobacco dependence is important for at least three reasons. First, several recent advances in dependence-based treatments for smoking appear to be effective, e.g., nicotine gum (6), clonidine (7), and brand fading (8). Knowledge of the prevalence of tobacco dependence and withdrawal would help determine the proportion of smokers who might benefit from such treatments. Second, smokers who attend formal treatment programs are usually dependent on tobacco (9). Knowledge of the prevalence of tobacco dependence would help anticipate the need for such smoking-cessation programs. Finally, indirect evidence suggests that the smokers who have quit are the less dependent smokers (10). If this selection bias continues, then future populations of smokers should contain higher proportions of dependent smokers. Serial determinations of the prevalence of tobacco dependence and withdrawal are necessary to test this hypothesis.

For these reasons, we surveyed the prevalence of tobacco dependence and withdrawal, defined according to accepted criteria, in a population-based sample.

METHOD

In 1974-1975, 116,980 households in defined census blocks in the Minneapolis-St. Paul metropolitan area were screened to find subjects to participate in the Multiple Risk Factor Intervention Trial (11). From these households, 30,401 men were screened, but only 703 men were entered into the trial. In 1980, we randomly sampled 5,000 of the households that contained ineligible men and found 1,184 men who were smokers and were willing to be in a study. After they gave informed consent, these men were randomly divided into four groups, each of which was given some combination of mailings, phone calls, and booklets about smoking and brief annual clinic visits. At the 2-year follow-up, 1,006 men were located, and they completed the survey that was the basis for this report.

At this follow-up, 6.9% (N=69) of the subjects had stopped smoking. Since the percentage of those who stopped did not differ across the four groups, data from all subjects were used in this analysis.

To determine the prevalence of tobacco dependence and withdrawal, we asked questions based on the *DSM-III* criteria as well as the criteria proposed by Fagerstrom (12) for tobacco dependence and our own criteria for tobacco withdrawal (13). We chose the latter two sets of criteria because, unlike most dependence and withdrawal criteria, they have been well validated (4, 12, 13). The Fagerstrom criteria for tobacco dependence include 1) the number of cigarettes smoked per day, 2) the number of milligrams of nicotine in each cigarette, 3) whether the smoker inhales, 4) whether the subject smokes more in the morning than in the afternoon and evening, 5) whether the subject smokes upon arising, 6) whether the first cigarette of the day is the most desirable, 7) whether it is difficult to refrain temporarily from smoking, and 8) whether the smoker smokes when ill. Our own criteria for tobacco withdrawal require the presence of at least four of the following in a smoker who has stopped for more than 24 hours: the first five of the *DSM-III* withdrawal symptoms, which we have already listed, plus increased appetite, impatience, somatic complaints (headache, dizziness, tremor, stomach or bowel problems), and insomnia.

RESULTS

The mean \pm SD age of the subjects was 51.1 \pm 6.4 years. Ninety percent (N=905) had completed high school, 58% (N=583) were professionals (occupational classes I–III) (14), and 46% (N=463) earned at least \$30,000 a year. The mean \pm SD number of cigarettes they smoked per day was 28.0 \pm 12.8, the mean \pm SD amount of nicotine per cigarette was 0.9 \pm 0.4 mg, and the mean \pm SD number of years they had smoked was 33.0 \pm 7.1. Forty-two percent (N=423) had tried to quit at least three times. These smoking habits are almost identical to those reported in previous surveys of middle-aged men (3) and, in fact, are quite similar to those obtained in surveys of all U.S. adults (3).

Ninety percent (N=905) of the smokers fulfilled *DSM-III* criteria for tobacco dependence. Sixty-one percent (N=614) had made an unsuccessful attempt to stop smoking, 21% (N=211) experienced tobacco withdrawal symptoms, and 23% (N=231) continued to smoke despite physical illness caused by smoking. Thirty-six percent (N=362) of the smokers fulfilled Fagerstrom's criteria for tobacco dependence (see table 1). The most prevalent *DSM-III* criterion was unsuccessful attempts to quit. Inhaling and smoking on arising were the most prevalent Fagerstrom criteria.

Eighty-seven percent (N=875) of the smokers reported that they had stopped smoking for at least 24 hours in the past. The mean \pm SD length of time since they had last quit for at least 24 hours was 67 \pm 86

TABLE 1. Prevalence of Tobacco Dependence According to the Fagerstrom Criteria in 1,006 Smokers

Criterion and Method of Scoring ^a	Score=0		Score=1		Score=2	
	N	%	N	%	N	%
Number of cigarettes smoked per day (<15=0, 16–25=1, >25=2)	181	18	301	30	523	52
Mg of nicotine per cigarette (<0.9=0, 0.9–1.2=1, >1.2=2)	543	54	312	31	151	15
Inhale (never=0, sometimes=1, always=2)	20	2	30	3	956	95
Smoke more in a.m. than p.m. (no=0, yes=1)	453	45	553	55		
Smoke upon arising (<30 minutes=0, >30 minutes=1)	332	33	674	67		
Most desirable cigarette (others=0, first one=1)	885	88	121	12		
Difficult to refrain temporarily (no=0, yes=1)	875	87	131	13		
Smoke when ill (no=0, yes=1)	573	57	433	43		

^aA score of more than 7 is required for a diagnosis of tobacco dependence.

months. The mean \pm SD duration of the last attempt to stop was 69 \pm 139 days. Ninety-three percent (N=814) quit abruptly. Ninety-six percent (N=840) stated that their memory of withdrawal symptoms was accurate. The self-reported accuracy of withdrawal symptoms and the number of withdrawal symptoms were not associated with the length of time since they had last stopped or the duration of the last period of nonsmoking.

Among those who had quit at some time, 21% (N=184) fulfilled *DSM-III* criteria and 46% (N=403) fulfilled our criteria for tobacco withdrawal (see table 2). The corresponding rates for all smokers (quitters and nonquitters) were 18% (N=181) and 37% (N=372). Craving for tobacco, restlessness, increased appetite, and impatience were the most common withdrawal symptoms.

The *DSM-III* definition of tobacco dependence was not concordant with the Fagerstrom definition of tobacco dependence or with either definition of tobacco withdrawal ($\kappa < .04$) (15). The Fagerstrom definition of tobacco dependence was modestly concordant with both definitions of tobacco withdrawal ($\kappa = .23$ and $.16$ for *DSM-III*'s and our definition, respectively). The *DSM-III* definition of withdrawal and our definition of withdrawal were fairly concordant ($\kappa = .44$).

DISCUSSION

The different definitions of tobacco dependence and withdrawal produced very different prevalence rates and showed little concordance. One possible reason for this lack of agreement is that one or more of the definitions are invalid. We know of no tests of the validity of the *DSM-III* definition of tobacco dependence. In addition, the fact that this definition classified 90% of the tobacco users in this study as depen-

TABLE 2. Prevalence of Tobacco Withdrawal Symptoms in 875 Smokers Who Had Quit Smoking in the Past

Criteria	N	%
<i>DSM-III</i>		
Used tobacco for at least several weeks	875	100
Smoked more than 10 cigarettes a day	770	88
Cigarette contained more than 0.5 mg of nicotine	735	84
At least four of the following within 24 hours of stopping smoking		
Craving for tobacco	639	73
Irritability	324	37
Anxiety	368	42
Difficulty concentrating	193	22
Restlessness	438	50
Headache	26	3
Drowsiness	70	8
Gastrointestinal disturbances	26	3
Authors' own criteria: at least four of the following within 24 hours of stopping smoking		
Craving for tobacco	639	73
Irritability	324	37
Anxiety	368	42
Difficulty concentrating	193	22
Restlessness	438	50
Increased appetite	420	48
Impatience	411	47
Somatic complaints	166	19
Insomnia	79	9

dent suggests that it is overinclusive and thus may lack diagnostic discriminability. The only validity test of the *DSM-III* definition of tobacco withdrawal that we know of found that three of the eight symptoms did not occur upon cessation of smoking (13).

On the other hand, several controlled, prospective studies have tested the validity of the Fagerstrom definition of tobacco dependence and of our definition of tobacco withdrawal (e.g., 4, 6, 9, 10). Of the 11 tests of the Fagerstrom definition of dependence, most have found that it predicts tolerance, withdrawal, smoking to obtain nicotine, relapse, and, most importantly, therapeutic response to nicotine gum (4). Likewise, seven studies (e.g., 4, 13, 16) have found that our own criteria for tobacco withdrawal are reliable, valid, and sensitive to both abstinence from tobacco and relief by nicotine gum. For these reasons, we believe that the prevalence rates given by the Fagerstrom definition of tobacco dependence and our definition of tobacco withdrawal are valid and conservative first approximations, whereas those calculated from the *DSM-III* criteria may not be valid.

According to Fagerstrom's and our definitions, one-third of smokers are either behaviorally dependent or physically dependent on tobacco (i.e., experience withdrawal symptoms). Since one-third of Americans smoke, approximately one in 10 Americans is presently tobacco dependent, according to our results. In comparison, no psychiatric diagnosis was present in more than 10% of the population in the Epidemiologic Catchment Area Program reports (1, 2).

Our results must be considered preliminary, as the generalizability and validity of our data can be questioned. The generalizability is uncertain because we

surveyed only middle-aged male smokers. Although replication of our prevalence rates in other age and sex groups is certainly needed, previous studies (e.g., 5, 13) have found that age and sex have little or no effect on tobacco dependence and withdrawal.

The validity of our estimates of tobacco withdrawal can be questioned for at least two reasons. First, our data are based on retrospective self-reports. However, the large majority of our smokers stated that their memory was accurate. More important, the time since the subjects had last quit smoking was not associated with an increase or decrease in the number of withdrawal symptoms they reported. Second, we decided to require that a smoker must have stopped smoking for at least 24 hours for withdrawal to be assessed. We made this rule to exclude halfhearted, temporary, or environmentally induced periods of abstinence. Also, many of the symptoms of withdrawal (e.g., insomnia) are not evident until several hours after cessation (5). However, our rule may have biased the results if it excluded smokers who had such severe withdrawal that they could not remain abstinent for 24 hours. We reasoned that, if anything, the rule would produce an underestimate of the prevalence of withdrawal.

In conclusion, our data indicate that many, but not all, smokers are behaviorally or physically dependent on tobacco. This result suggests that a considerable minority (20%–50%) of smokers may benefit from formal treatment programs or dependence-based treatments. Our data also indicate that the *DSM-III* criteria for tobacco dependence are overinclusive and are not concordant with other measures of tobacco dependence and withdrawal. These results suggest that the *DSM-III* criteria for tobacco dependence need to be reformulated.

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Psychiatric and Medical Diagnoses as Risk Factors for Mortality in Psychiatric Patients: A Case-Control Study

George Winokur, M.D., and Donald W. Black, M.D.

On the basis of a case-control study, the authors conclude that former psychiatric inpatients are more likely than control subjects to die of both natural and unnatural causes within 2 years of discharge. Patients who committed suicide were more likely to have had a diagnosis of affective disorder (unipolar depression) or alcoholism. Those who died of natural causes were more likely to have been admitted with medical diagnoses; no specific psychiatric diagnoses were associated with these deaths. It is doubtful that medical illnesses caused psychiatric syndromes such as depression in these inpatients. Psychiatric and medical illnesses combined may increase a patient's likelihood of seeking psychiatric help and entering the hospital.
(*Am J Psychiatry* 1987; 144:208-211)

Considerable evidence shows that former psychiatric inpatients have significantly higher death rates than expected for the age- and sex-matched general population (1). Premature death rates from both natural and unnatural causes are particularly high within the first 2 years of discharge from the hospital. Accident and suicide death rates are significantly higher for both men and women; men show a marked excess of

deaths from influenza and pneumonia, and women show a significant excess of deaths from cancer, heart disease, and respiratory causes.

Several factors may affect both natural and unnatural deaths. For example, medical illness at the time of admission to the hospital may contribute to these two kinds of deaths. Conceivably, medical illness may occur more frequently in conjunction with certain psychiatric diagnoses; some patients may be admitted because of a combination of psychiatric and medical illnesses. Furthermore, psychiatric disorders may adversely influence a medical disease, increasing both its morbidity and mortality.

Certain illnesses (e.g., Huntington's disease and cancer) are associated with a high suicide rate (2, 3). Consequently, one might question whether medical diagnoses at the time of admission are related to suicide within 2 years after discharge. Finally, certain kinds of psychiatric diagnoses may be overrepresented in patients who have died of natural causes.

This study used a different methodology from that which is usually found in psychiatry. The control was for course (in this case, natural and unnatural mortality) rather than diagnosis. Obtaining similar findings on natural and unnatural mortality by using different diagnostic groups would be difficult because huge numbers of patients in each diagnostic group would be required.

METHOD

Of 5,412 patients admitted to the Psychiatric Hospital of the University of Iowa between January 1,

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1972, and December 31, 1981, 73 died within 2 years of discharge from unnatural causes and 115 from natural causes. We obtained this information by linking the death certificate records of Iowans in Iowa with the records of psychiatric admissions; however, we had no way of following ex-patients who had moved from Iowa and died in other states. The methodology of the record linkage is described more fully elsewhere (1).

Psychiatric diagnoses were made by a faculty member and a resident at the time of hospital discharge and were based on the *International Classification of Diseases, 9th Revision* (4), which was the diagnostic system used in the hospital during the 1970s.

We matched the 73 patients who had died unnatural deaths and the 115 who had died of natural causes with patients who had survived by taking the next admitted patient of the same sex and within 5 years of age. We found control subjects for all of the patients who died unnatural deaths and all but four of the patients whose deaths were from natural causes (N=111 natural death control subjects).

Occasionally an effort is made to conceal a suicide as a natural death. We examined this possibility in a subsample of 2,054 patients: 136 natural deaths occurred in a 4- to 5-year period, and from a perusal of records only one or two could possibly have been suicides. Charts were evaluated to determine the presence of medical illness diagnoses. A medical diagnosis was recorded if it was included as a discharge diagnosis. Medical illnesses were separated into "significant" and "other" categories. Significant medical illnesses were those that could lead to disability or death; examples included cardiovascular disease, cancer, chronic obstructive pulmonary disease, and kidney disease. Other medical illnesses included such diseases and conditions as easily managed diabetes, cystitis, hernia, uterine fibroid, and congenital anomalies.

RESULTS

Unnatural Deaths

Fifty-four (74%) of the unnatural deaths were suicides. The remaining 19 unnatural deaths (26%) were accidental. Table 1 compares medical and psychiatric diagnoses between the control subjects and the patients who suffered unnatural deaths. In addition, patients who specifically committed suicide are compared with their matched control subjects. The mean age of patients who suffered an unnatural death was 35.5 years (range, 18–76).

Table 1 shows significant differences in psychiatric diagnoses. Twenty-eight patients (52%) who committed suicide had affective disorders, compared with 18 control subjects (33%) ($\chi^2=3.79$, $df=1$, $p=.05$). Drug and alcohol diagnoses were found in twice as many of the patients who committed suicide, but this finding did not reach significance ($\chi^2=2.0$, $df=1$). Personality

disorders were more frequent among the control subjects ($\chi^2=10.57$, $df=1$, $p=.005$). The combined diagnoses of affective disorder and alcohol and drug abuse were far more frequent among the patients who committed suicide ($\chi^2=6.28$, $df=1$, $p=.025$). Notably, the suicide and control groups each included six patients with a diagnosis of bipolar affective disorder, so the difference between the suicide and control groups was accounted for by an excess in unipolar depression. In fact, the unipolar depressive diagnoses alone were significantly more frequent for the suicide patients than the control subjects ($\chi^2=4.29$, $df=1$, $p=.05$). Finally, there were no reliable differences in either significant medical diagnoses or other medical diagnoses between the unnatural death patients and their control subjects or between the suicide patients and their control subjects.

Of the 54 patients who committed suicide, 27 were women and 27 men. Fourteen of the men were under the age of 30 at the time of the suicide, in contrast to only seven of the women. This difference in age at suicide almost reached significance at the .05 level ($\chi^2=3.82$). Women were more likely to commit suicide between ages 30 and 49 (17 women versus nine men). After age 50, four men and three women committed suicide.

Natural Deaths

Women accounted for 55% of the 115 natural deaths and men for 45%. The cause of death was cancer for 23 patients, diabetes for four, heart disease for 43, cerebrovascular accidents for seven, influenza/pneumonia for seven, other respiratory disease for six, and other medical illness for 25. The mean age of the patients who died of natural causes within 2 years of discharge was 60 (range, 19–97). Table 1 compares medical and psychiatric diagnoses for control subjects and patients who died natural deaths.

There were no significant differences between psychiatric diagnoses of the patients who died natural deaths and the diagnoses of the control subjects. Organic mental disorders were more frequent among those who died a natural death, but this failed to reach significance ($\chi^2=2.45$, $df=1$). Also, the natural death patients had fewer affective disorder diagnoses than did the control subjects ($\chi^2=3.51$, $df=1$).

The major findings have to do with significant medical diagnoses. Fifty-five patients (48%) with natural deaths were diagnosed with a significant medical disorder, as opposed to only 19% of the control subjects ($\chi^2=13.87$, $df=1$, $p=.0005$). Control subjects showed more other medical diagnoses than did patients who died a natural death ($\chi^2=3.89$, $df=1$, $p<.05$). For all medical diagnoses combined, patients who died a natural death (N=67 [58%]) had a significantly higher rate of such diagnoses than did control subjects (N=43 [39%]) ($\chi^2=8.62$, $df=1$, $p<.005$).

Table 2 presents the association of organic mental disorders with significant medical illness for patients

TABLE 1. Medical Illness in Psychiatric Patients Who Died Within 2 Years of Hospital Discharge

Diagnosis	Unnatural Causes								Natural Causes			
	All Unnatural Death Victims (N=73)		Control Subjects (N=73)		Suicide Victims (N=54)		Control Subjects (N=54)		All Natural Death Victims (N=115)		Control Subjects (N=111)	
	N	%	N	%	N	%	N	%	N	%	N	%
Medical	11	15	12	16	7	13	7	13	67	58	43	39
Significant	7	10	9	12	4	7	5	9	55	48	21	19
Other	4	5	3	4	3	6	2	4	12	10	22	20
Psychiatric												
Organic mental disorder	3	4	6	8	1	2	1	2	40	36	28	25
Schizophrenia	12	16	12	16	10	19	10	19	11	10	7	6
Affective disorder	32	44	21	28	28	52	18	33	33	27	45	41
Neurosis	3	4	6	8	2	4	4	7	5	4	5	5
Alcoholism, drug abuse	12	16	8	10	7	13	4	7	12	10	10	9
Adjustment reaction	3	4	0	0	0	0	0	0	4	3	2	2
Personality disorder	6	8	15	21	2	4	14	26	3	3	6	5
Anorexia nervosa	0	0	0	0	0	0	0	0	3	3	0	0
Other	0	0	0	0	4	7	3	6	2	2	4	4
Undiagnosed	2	3	2	3	0	0	0	0	2	2	4	4
No psychiatric illness	0	0	3	4	0	0	0	0	0	0	0	0

TABLE 2. Association of Organic Mental Disorder With Significant Medical Illness in Psychiatric Patients Who Died of Natural Causes Within 2 Years of Hospital Discharge

Group	Organic Mental Disorder	
	Yes	No
All patients (N=115)		
Significant medical illness	27	28
No significant medical illness	12	48
Patients over 60 years (N=66)		
Significant medical illness	22	13
No significant medical illness	12	19

who died of natural causes. For all patients who died, there was an excess of significant medical illness in those patients who had organic brain syndromes ($\chi^2=10.84$, $df=1$, $p<.001$). Among patients over 60 years of age, there was a similar excess of patients with both organic mental disorders and significant medical illness ($\chi^2=3.84$, $df=1$, $p<.05$). This difference was not only associated with age. In fact, the standardized observed/expected mortality ratio is 1.2 in patients over 60, whereas it is 1.5 in the younger group of patients. This observed/expected figure is simply a calculation of how many in the groups would be expected to have both organic mental disorders and significant mental illnesses by chance. Thus, the ratio, in fact, is higher for the total group than for the group over 60.

We evaluated the influence of age and sex on the natural deaths. In patients under 50, men were more likely than women to have had a medical illness (79% [N=9 of 13] vs. 21% [N=3 of 14]) ($\chi^2=6.24$, $df=1$, $p=.025$). In the over-50 group, however, men who died during the 2-year follow-up were less likely to have had any medical illness (41% [N=15 of 37] vs. 63% [N=32 of 51]) ($\chi^2=4.25$, $df=1$, $p<.05$).

To investigate whether any specific psychiatric diagnosis other than organic mental disorder was associated with natural death, we removed all matches

between psychiatric patients and control subjects in which one or the other or both had an organic mental disease. This left 60 matches. No specific psychiatric diagnosis was found to be associated with natural mortality. Thus, 9% (N=5) of the deceased and 6% (N=4) of the control subjects had schizophrenia; 5% (N=3) of the deceased and 9% (N=5) of the control subjects had bipolar illness; 19% (N=11) of the deceased and 20% (N=12) of the control subjects had unipolar depressive illness; 10% (N=6) of the deceased and 8% (N=5) of the control subjects had anorexia, drug abuse, or alcoholism; and 17% (N=10) of the naturally deceased and 17% (N=10) of the control subjects had a diagnosis of neurosis, adjustment disorder, personality disorder, other psychiatric illness, or undiagnosed psychiatric disorder. No psychiatric diagnosis separated the natural death patients from the control subjects.

DISCUSSION

Within a psychiatric hospital population, affective disorders, alcoholism, and other drug abuse were overrepresented in patients who committed suicide. Robins et al. (5) found that in their population, alcoholism and affective disorders were the two most frequent diagnoses of patients who committed suicide. Both of these disorders are common in the community, suggesting that the increased suicide rates for alcoholism and affective disorders may simply be linked to the frequency of occurrence of the disorders. However, with the methodology of a case-control study such as the present one, the evidence favors the possibility that these two illnesses—alcoholism and affective disorder—put one at higher risk for suicide. Interestingly, only the unipolar depressed patients (including patients with depressive neuroses), and not the bipolar depressed patients, were overrepresented in the suicide

group. This finding represents another clinical difference between the two major forms of primary affective disorder.

Certain medical illnesses (e.g., cancer and Huntington's disease) are associated with suicide, but medical diagnoses did not account for suicide outcomes in the psychiatric patients. Medical illness was as frequent in the control subjects as in the patients who committed suicide, suggesting that the psychiatric illness itself was the major factor leading to the suicide.

Patients who died of natural causes during follow-up were more likely than control subjects to have had significant medical illnesses at the time of their hospital admission, and this raises many questions. Could psychiatric illness adversely affect medical illness and thus account for the high mortality rate (188 observed deaths/59.9 expected deaths=standardized mortality ratio of 3.14, $p<.001$) in hospitalized psychiatric patients (1)? Psychiatric illness might delay the recognition of medical illness and consequently shorten the course of the medical illness. Similarly, psychiatric patients may not take adequate care of themselves and so hasten their own death. To adequately address the reason for the high mortality rate requires a systematic follow-up of a group of psychiatrically ill persons with medical illness and a comparison group of non-psychiatrically-ill persons with medical illness. If an adverse effect exists, the psychiatrically ill persons with medical illness would die earlier. Although our study did not address this question, another study did. Goldberg et al. (6), using a matched case-control analysis, compared medically ill or deceased subjects with control subjects on the variables of depressive symptoms and mood, which had been measured and collected in a population study 6–12 months earlier. No relationship between depressive symptoms or depressive mood and subsequent medical illness or death was observed. However, we should note that these were not psychiatrically ill patients but simply subjects who scored high on symptom lists and mood scales.

Alternatively, is it possible that medical illness produces psychiatric illness? If this were true, it seems unlikely that this phenomenon would be seen in all psychiatric diagnoses; rather, it might be associated with a particular psychiatric diagnosis, such as a secondary depression. An earlier study by Stewart et al. (7) showed considerable depression in patients who had major medical illnesses. The present study showed no differences in depression or other diagnoses between the deceased psychiatric patients and the control subjects. Thus, the current study gives no support to the idea that medical illness causes specifically diagnosed psychiatric illness in an inpatient population. In order to accept the possibility that medical illness produces a nonspecific effect, there must be a common etiology in part for all psychiatric illnesses.

In the 60 comparisons between deceased psychiatric patients who died of natural causes and control subjects (where neither had an organic mental illness), no

difference in the amount of unipolar depression or any other diagnosis was indicated. Natural mortality seems unrelated to a specific diagnosis of depression.

That there is a better than chance association among morbidity, physical illness, and psychiatric illness seems undeniable (8). This is particularly true in a university hospital with a high proportion of complicated cases, but these associations are found in general practice, psychiatric inpatient services, day hospitals, and outpatient clinics (9). We may be dealing with an ascertainment phenomenon. When patients have two types of illnesses, physical and psychiatric, their "social burden" may be greater, making it more likely that they will be treated in a psychiatric facility; that is, the combination increases the probability that treatment will be sought.

We would predict that those who sought treatment and then died during follow-up would have been more severely ill. We evaluated the naturally deceased patients and control subjects on the variable of single versus multiple medical diagnoses. Of those deceased patients who had any medical diagnosis, 74% had more than one, but of the control survivors who had any medical diagnosis, only 44% had more than one ($\chi^2=6.40$, $df=1$, $p<.025$). Thus, deceased patients were more likely to have had multiple medical disabilities.

From the data one might conclude that psychiatric illness preponderantly leads to unnatural death and physical illness to natural death in psychiatric patients. Although medical illness probably does not induce a specific psychiatric condition, its presence may increase the likelihood that a psychiatrically ill patient will be hospitalized. Thus, a serious workup for medical illness should be mandatory for the psychiatric inpatient. A cursory examination for the sake of the record will not do.

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Prognostic Validity of the Dexamethasone Suppression Test: Results of a Six-Month Prospective Follow-Up

Mark Zimmerman, B.A., William Coryell, M.D., and Bruce Pfohl, M.D.

In a 6-month prospective follow-up study, the authors located and interviewed 165 (88.2%) of 187 primary unipolar depressed inpatients to whom a 1-mg dexamethasone suppression test (DST) had been given during their first week of hospitalization. Longitudinal ratings of symptoms over the follow-up period and 6-month cross-sectional ratings on the Hamilton Rating Scale for Depression, the Beck Depression Inventory, and the Global Assessment Scale were obtained for each patient. The authors also collected information on rehospitalization after discharge from the index episode. Baseline DST results were not associated with any of the outcome variables.

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In a previous report (1), we examined the relationship between dexamethasone suppression test (DST) results and family history of specific psychiatric disorders, such psychosocial variables as life events and social support, such clinical features as suicide attempts and endogenous symptoms, and such demographic characteristics as age and marital status and found that nonsuppressors had a more endogenous clinical profile than suppressors. In the present paper, we focus on the predictive validity of the DST and examine its relationship to course of illness during a 6-month prospective follow-up.

METHOD

The patients were described in detail in our previous report (1). Briefly, from August 1981 until July 1983, we recruited a consecutive series of patients diagnosed as having DSM-III major depressive disorder and admitted to the psychiatric inpatient unit at the University of Iowa Hospitals and Clinics. All patients were

18 years of age or older and had none of the medical and pharmacologic exclusion criteria for the DST described by Carroll et al. (2). We also excluded patients taking carbamazepine (3) and insulin-dependent diabetics (4). All patients gave informed consent before participating in the study.

During the first week of hospital admission (mean = 2.5 days after admission), the patients were given 1 mg of dexamethasone at 11:00 p.m., and blood was sampled the next day at 8:00 a.m. and 4:00 p.m. Cortisol level was measured by radioimmunoassay with the specific cortisol antiserum obtained from Damon Diagnostics, Needham Heights, Mass. There was no cross-reactivity with dexamethasone, progesterone, testosterone, or 11-deoxycortisol, and the intra-assay and interassay coefficients of variation were 12.2% and 11.1%, respectively, at concentrations around the cutoffs to classify patients as nonsuppressors. The same procedure used with the depressed patients was used to administer the DST to 33 normal control subjects. Because the test's specificity was 97% with a cutoff of 5 µg/dl and 91% with a cutoff of 4 µg/dl, nonsuppression was defined as a serum cortisol level greater than 5.0 µg/dl at either sampling.

Raters blind to the DST results contacted patients 6 months after entry into the study and quantified psychopathology in a fashion developed by the Clinical Branch of the NIMH Collaborative Study of the Psychobiology of Depression. For each week of the follow-up, raters determined whether patients had felt like their usual, normal selves and rated the presence or absence of the eight DSM-III part B criteria symptoms for major depressive disorder for each postdischarge week. To do this, the raters inquired about change points, i.e., dates when definite improvement or worsening took place. They assigned each week a symptom rating on a 4-point scale. A week without depressive symptoms was assigned a score of 1. The presence of one or two criteria depressive symptoms resulted in a score of 2. A score of 3 reflected the presence of three or four criteria symptoms, and the presence of five or more symptoms was scored 4. The raters also determined the type and amount of treatment each patient received after discharge from the index hospitalization and administered the Hamilton Rating Scale for Depression (5), the Beck Depression Inventory (6), and the Global Assessment Scale (7) to

Received Feb. 11, 1986; revised May 27, 1986; accepted Aug. 6, 1986. From the Department of Psychiatry, University of Iowa. Address reprint requests to Mr. Zimmerman, Department of Psychiatry, University of Iowa College of Medicine, 500 Newton Rd., Iowa City, IA 52242.

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each patient during the week before the follow-up interview.

To make use of the most outcome data possible, we determined the mean symptom rating across all weeks of the follow-up for each patient and calculated the mean of these values for the suppressors and nonsuppressors. We also examined four different definitions of sustained recovery. Following the convention adopted by the Collaborative Study of the Psychobiology of Depression, we defined sustained recovery as a period of at least 8 consecutive weeks in which the patient had at most one or two depressive symptoms. Our second definition of sustained recovery required that the patient also feel like his or her usual self during the 8 weeks in which he or she had only one or two depressive symptoms. Third, consistent with our prior reports on the 6-month outcome after ECT (8, 9), we defined recovery as an 8-week period entirely free of symptoms. Finally, we defined sustained recovery as an 8-week period during which the patient felt like his or her usual self, regardless of the level of depressive symptoms.

We assessed the reliability of our follow-up procedure in two ways (10). Twenty-one depressed patients were interviewed once a month after their discharge from the hospital until their scheduled 6-month follow-up interview. The monthly interviews followed the same format as described for the 6-month interview. Audiotapes of these interviews were rated to assess reliability in an observer/rater paradigm. An independent rater interviewed each patient 6 months after the index admission and assessed symptoms for the entire postdischarge period. Thus, we examined the test-retest reliability of follow-up assessments by comparing information obtained from the monthly interviews with the data collected at the 6-month interview. We found excellent agreement for audiotape ratings of the monthly interviews and generally good agreement between the monthly and the 6-month interviews (10).

RESULTS

Of the 187 primary unipolar depressed inpatients who were given the DST during their first week of hospitalization, 60 (32.1%) were nonsuppressors. Four patients (2.1%) died during the 6-month follow-up period (one by suicide), 14 (7.5%) could not be located, and four (2.1%) refused to be interviewed; thus, we completed follow-up interviews for 165 (88.2%) of the 187 patients. The rate of completed follow-up interviews was nonsignificantly higher in the suppressors than in the nonsuppressors (91.4% or $N=116$ versus 81.7% or $N=49$, respectively; $\chi^2=3.67$). The majority of the 165 patients were women (72.9%, $N=121$), high school graduates (80%, $N=133$), and married (46.4%, $N=77$). The mean \pm SD age of the sample was 40 ± 16.2 years.

During the follow-up interval, there were no differ-

TABLE 1. Rehospitalization and Recovery During 6-Month Follow-Up for 165 Unipolar Depressed Patients Who Had Been DST Suppressors ($N=116$) or Nonsuppressors ($N=49$)

Outcome	Suppressors		Nonsuppressors		χ^2 (df=1)
	N	%	N	%	
Rehospitalized	30	26.1	17	34.7	1.24
Sustained recovery for 8 weeks					
One or two depressive symptoms	71	62.3	35	68.6	0.62
One or two depressive symptoms and back to normal self	57	50.0	24	47.0	0.12
No depressive symptoms	37	32.5	18	36.0	0.20
Back to normal self	62	54.4	30	58.8	0.28

ences between suppressors and nonsuppressors in rehospitalization or recovery rates (table 1). In addition, suppressors and nonsuppressors did not differ by mean \pm SD weekly follow-up score (2.5 ± 1.0 and 2.4 ± 1.0 ; $t=0.23$), 6-month Hamilton ratings (8.7 ± 8.5 and 8.2 ± 7.5 ; $t=0.41$), 6-month Beck Depression Inventory scores (13.2 ± 13.2 and 11.3 ± 10.3 ; $t=0.89$), or 6-month Global Assessment Scale ratings (61.2 ± 17.1 and 63.7 ± 16.7 ; $t=0.85$).

DISCUSSION

We did not find an association between DST results obtained during the first week of hospitalization and 6-month posthospital course. These negative findings are consistent with the findings from two other studies of the DST's prognostic validity. Targum (11) followed up 86 unipolar depressed patients meeting *DSM-III* criteria for melancholia and found that relapse within 6 months of hospital discharge was nonsignificantly more frequent among nonsuppressors than among suppressors. In a study completed before the present investigation, we found that DST results did not predict course during a 6-month follow-up of 42 depressed inpatients who received ECT (8). Thus, three studies of short-term prognosis have failed to find an association between admission DST results and outcome.

In our previous article (1), we examined the validity of the DST in terms of predictions consistent with the construct of endogenous depression. Following the Washington University model of establishing diagnostic validity (12), we suggested that a valid marker of endogenous depression should demonstrate significant relationships with certain demographic, clinical, and family history variables. Specifically, we indicated that patients with endogenous depression (nonsuppressors on the DST) should be characterized by a low morbid risk of alcoholism and antisocial personality in their first-degree relatives, a stable marital history, good social support, a low level of psychosocial stress, normal premorbid personality, and high scores on

symptom severity scales. We did not include a prediction about prognosis because no consistencies have emerged from the literature regarding the prognostic validity of endogenous subtyping (13–15). Theoretically, it is not apparent what predictions should be made. Should endogenous depression, a more severe illness than nonendogenous depression (16), be associated with a poorer postdischarge outcome? Or should endogenous depression be characterized by distinct remissions, with a return to the normal, asymptomatic premorbid state until the next episode, which occurs a long time afterward?

The results of our validation study of the DST (1) indicated that in comparison to normal suppressors, nonsuppressors were older; had less premorbid personality disorder, better social support, less frequent marital separations or divorce, and fewer stressful life events; were less likely to make a nonserious suicide attempt during their index episode; had fewer dysfunctional attitudes; and had a lower rate of treated alcoholism and antisocial personality in their first-degree relatives. We originally concluded that our only negative finding was the lack of association between DST results and a family history of depression. In fact, we were mistaken to predict that nonsuppressors should have a higher morbid risk of depression in their first-degree relatives, because nonendogenous depression is probably just as familial as endogenous depression (17). Thus, our only two negative findings regarding the validity of the DST (family history of depression and 6-month course) should have been expected.

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Suicide and Homicide in the United States: An Epidemiologic Study of Violent Death, Population Changes, and the Potential for Prediction

Paul C. Holinger, M.D., M.P.H., Daniel Offer, M.D., and Eric Ostrov, Ph.D.

The authors found significant positive correlations between the suicide and homicide rates for 15–24-year-olds and the proportion of 15–24-year-olds in the U.S. population from 1933 to 1982.

Significant negative correlations were found for most adult age groups (35–64 years). Since future numbers of adolescents and adults can be estimated on the basis of current population data for children and preadolescents, the epidemiologic patterns for suicide and homicide may be predictable for certain age groups. However, methodologic problems are inherent in using national mortality and population data, and many years are necessary to evaluate such epidemiologic propositions.

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Suicide and homicide are the fourth leading cause of death in the United States, following cardiovascular disease, cancer, and accidents, respectively (1). One of the most important aspects of suicide and homicide subjected to recent scientific scrutiny is their predictability (2–13). In previous studies (12, 13) we found significant positive correlations between the suicide and homicide rates for adolescents and young adults (15–24-year-olds) and the proportion of 15–24-year-olds in the population of the United States; i.e., as the proportion of 15–24-year-olds increased in the United States, the rates for suicide and homicide increased. An older age group (65–69-year-olds) was also studied, and the opposite trend was found: as the proportion of

65–69-year-olds increased, their suicide rate decreased (12). Inasmuch as the future number of adolescents and adults can be estimated years ahead on the basis of current population data for children and preadolescents, these results suggested that suicide and homicide rates might be predictable for certain age groups.

Detailed reviews of the literature on suicide and homicide have been presented elsewhere (2, 11–13), but several themes should be noted here. Suicide and homicide (homicide mortality rate refers to those killed, not to the killers) may be related in that both may be types of self-inflicted death (14, 15). Suicide is the most overt type, and homicide may be a more subtle manifestation of self-destructive tendencies and risk taking (2). Homicide may be “victim precipitated” and self-inflicted in that some victims may provoke their own deaths by “being in the wrong place at the wrong time” (14, 15). Positive relationships between population increases and upsurges in the rates of various forms of violent death have been found by some researchers (10, 16, 17) but not confirmed by others (18–20). Cohort studies (21–23) have supported the findings of recent increases in suicide rates among young cohorts followed since about 1950, but these studies have not systematically related such findings to population shifts in those age groups.

The work of Easterlin (7), Brenner (3, 4), and others (8–10, 24), which included extensive research of population and economic variables, began to suggest the potential for prediction of suicide and homicide rates. An emerging conceptualization involves the interaction of these variables (e.g., good economic conditions leading to a higher birth rate and subsequent population changes), by which it is possible to understand violent death rates from an epidemiologic view.

The purpose of the present study was to expand our own previous results and ask, What is the relation between suicide and homicide rates and proportion of population for other age groups? and Might it be possible to predict fluctuations in suicide and homicide for specific age groups from the population model?

METHOD

As detailed elsewhere (2), two major types of methodologic problems occur when using national mortal-

Received March 3, 1986; accepted Aug. 7, 1986. From the Department of Psychiatry, Institute for Psychosomatic and Psychiatric Research and Training, Michael Reese Hospital and Medical Center, Chicago; and the Center for Suicide Research and Prevention, Department of Psychiatry, Rush-Presbyterian-St. Luke's Medical Center. Address reprint requests to Dr. Holinger, Rush-Presbyterian-St. Luke's Medical Center, 1725 West Harrison St., Chicago, IL 60612.

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ity data to study violent death patterns: 1) under- and overreporting and 2) data classification problems. Underreporting may cause reported suicide data to be at least two or three times lower than the real figures (24–26). With respect to homicide, the rates measure those killed; homicide rates for the various age groups say nothing, strictly speaking, about the age or numbers of the killers.

Two types of data classification problems exist. One involves the changes in classification at the national level over time. There has been little change over the century in federal classification for suicide and homicide (2). The second type of data classification problem concerns classification at the local level, e.g., inconsistencies in coroners' reports from one geographic locality to another.

The data used in this report are for the complete population, not samples; they include all suicides and homicides among the indicated age groups that occurred in the United States. Mortality data before 1933 are not included because it was only after 1932 that all states were incorporated into the national mortality statistics (Alaska was added in 1959 and Hawaii in 1960). The data used are mortality rates (deaths per 100,000 population), not simply numbers of deaths. Although it might be assumed that the number of deaths from a particular cause will increase with an increase in the population, the mortality rates do not necessarily increase with an increase in population because the denominator is constant, i.e., 100,000 population.

The correlations were derived by using the residual scores described previously (13). The possibility that the correlations are artifacts due to changes in federal classifying of suicide and homicide is unlikely; the comparability ratios for suicide and homicide have been rather consistent over the decades (2). However, the possibility exists that another variable is involved, i.e., period effects due to economic trends (period effects involve changes in rates of mortality or illness during a particular historical period [27]). In the early 1930s the suicide and homicide rates were at their peaks, probably because of the economic depression. These rates decreased for several years afterward, reaching low points during the early 1940s (World War II). During the time of this decrease in rates, however, the population of adults 35–64 years in the United States increased steadily. These economic shifts could therefore be seen as having contributed to the inverse correlations, and the population variable would have had a coincidental rather than etiologic relationship to the violent death rates.

RESULTS

Table 1 presents the correlation coefficients for the associations between the suicide and homicide rates for each of five age groups and the ratio of the population of that age group to the total population in

TABLE 1. Correlations Between Suicide and Homicide Rates and Percentage of U.S. Population for Five Age Groups, 1933–1982^a

Age	Correlation With Percentage of U.S. Population			
	Suicide Rate		Homicide Rate	
	r	p	r	p
15–24 years	.34	<.01	.41	<.001
25–34 years	.00	n.s.	-.01	n.s.
35–44 years	-.52	<.001	-.68	<.001
45–54 years	-.05	n.s.	-.47	<.001
55–64 years	-.32	<.05	-.25	<.05

^aSources of suicide and homicide data: references 28 (for 1933–1953), 29 (for 1954–1960), and 30 (for 1961–1979) and unpublished data from the National Center for Health Statistics (for 1980–1982). Sources of population data: references 29 (for 1933–1960) and 30 (for 1961–1979) and unpublished data from the National Center for Health Statistics (for 1980–1982).

the United States for 1933–1982. The suicide rate showed a significant positive correlation with the population ratio of the 15–24-year-olds; that is, the suicide rate increased among 15–24-year-olds as the proportion of 15–24-year-olds in the total U.S. population increased, and the rate decreased as the proportion of 15–24-year-olds decreased. The suicide rates showed significant inverse correlations with the shifts in population ratios for 35–44- and 55–64-year-olds; i.e., increases in the proportions of 35–44- and 55–64-year-olds in the United States were associated with decreases in the suicide rates for those groups. The correlation between the suicide rate and population ratio for 25–34-year-olds was not significant. A similar pattern was found for homicide rates: a significant positive correlation between the homicide rate and population ratio of 15–24-year-olds, a nonsignificant correlation for 25–34-year-olds, and significant inverse correlations for 35–44-, 45–54-, and 55–64-year-olds.

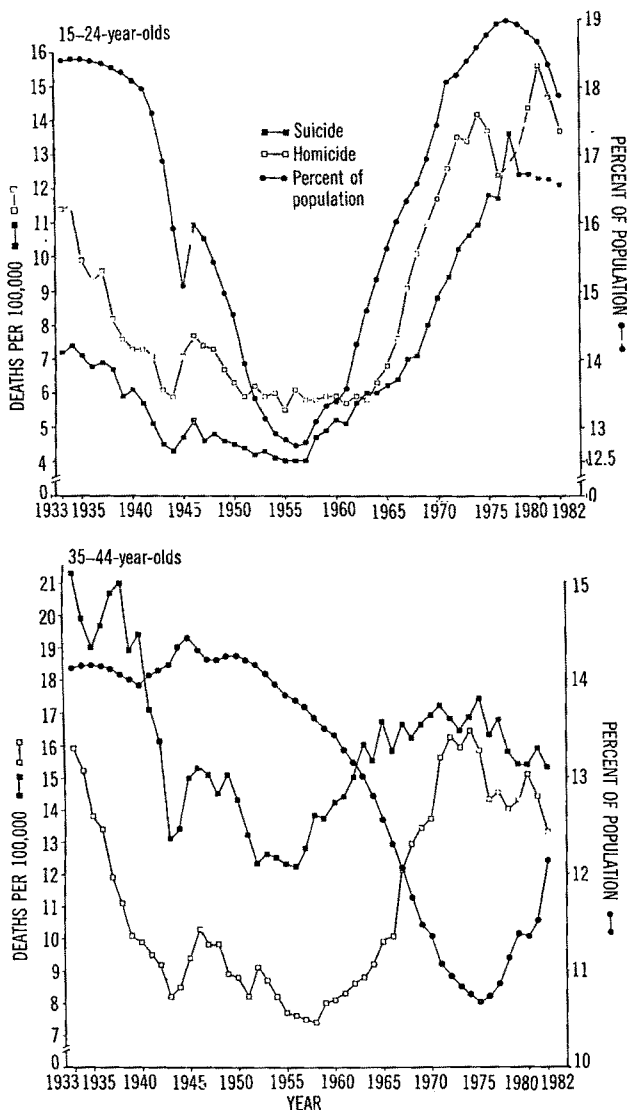
Figure 1 depicts the differences between the younger and adult age groups. The top of figure 1 shows the changes over time in suicide and homicide rates for 15–24-year-olds and the proportion of 15–24-year-olds in the United States during 1933–1982. The mortality rates and proportion of 15–24-year-olds in the population can be seen to be rather parallel. The bottom of figure 1 shows the relationship between changes in suicide and homicide rates and population changes among 35–44-year-olds, and the mortality rates have trends somewhat opposite to the population changes.

DISCUSSION

Suicide, Homicide, and Population Shifts

The data suggest that increases in the proportion of 15–24-year-olds are accompanied by increases in their suicide and homicide rates, whereas increases in the

FIGURE 1. Suicide and Homicide Rates and Percentage of U.S. Population for 15–24-Year-Olds and 35–44-Year-Olds, 1933–1982^a



^aSources of suicide and homicide data: references 28 (for 1933–1953), 29 (for 1954–1960), and 30 (for 1961–1979) and unpublished data from the National Center for Health Statistics (for 1980–1982). Sources of population data: references 29 (for 1933–1960) and 30 (for 1961–1979) and unpublished data from the National Center for Health Statistics (for 1980–1982).

proportion of 35–64-year-olds are accompanied by decreases in their suicide and homicide rates. These findings may have important psychiatric and predictive implications and, with other studies (3–5, 10), call into question Henry and Short's hypothesis that suicide and homicide are inversely related (6). However, the data and resulting hypotheses regarding prediction should be viewed with caution because of the methodologic problems inherent in using national mortality data and the number of years required to adequately test such epidemiologic propositions over time.

The results in table 1 may be understandable if the

correlations are viewed as shifting from positive to negative as age increases. At least three levels of interpretation seem possible and need to be subjected to further hypothesis testing: an epidemiologic-sociological level, a psychodynamic-clinical level, and a nosological level.

On the epidemiologic-sociologic level, suicide and homicide rates may increase with increases in the proportion of 15–24-year-olds for a variety of reasons; for instance, with increased competition for jobs, college positions, and academic and athletic honors come an increased number of adolescents who fail to get such places (12, 13). Such reasoning is consistent with Barker and Gump's extensive data (31, 32) on large and small schools. In addition, the younger members of the 15–24-year-old group may be the least powerful and attractive force in society with respect to political pressure, jobs, and so on. On the other hand, adults in the 35–64-year-old groups are much more powerful politically and are more attractive employees because of more experience and schooling. Thus, the population increases in the adult age groups may lead not so much to increased competition and failure but, rather, to more economic benefits (greater and more successful pressure on government and union leaders to enlarge the job market, obtain more health services, etc.). Therefore, suicide and homicide rates would decrease with the increased population ratio in the adult age groups.

Briefly, explanations for the two other levels follow somewhat similar reasoning. For example, on the psychodynamic-clinical level, depressed adolescents with marginal ego capacities and an inadequately internalized sense of self-esteem may be at increased risk of suicide when there are more adolescents, since there is heightened competition for much-needed external sources of self-esteem (e.g., academic honors, places on athletic teams). On the nosological level, when the proportion of young people is high, adolescents with thought disorders or major affective disorders may be at greater risk of suicide not only for the reasons already presented but also because of a relative decrease in the psychiatric services available for diagnosis and treatment.

Potential Prediction: Psychiatric and Public Health Implications

It has been suggested (12, 13, 24) that as the absolute number and the proportion of adolescents and young adults began to decrease in the late 1970s and 1980s, the suicide rate for that age group (which had been increasing over the previous 20 years with the increase in the young population) would begin to level off and decrease. This hypothesis has some support from recent data on the suicide rates for 15–24-year-olds in the United States: 1977, 13.6 deaths/100,000 (33); 1978, 12.4 deaths/100,000 (33); 1979, 12.4 deaths/100,000 (33); 1980, 12.3 deaths/100,000 (34); 1981, 12.3 deaths/100,000 (34); 1982, 12.1

deaths/100,000 (1); and 1983, 11.9 deaths/100,000 (National Center for Health Statistics, unpublished data). The 1977 suicide rate of 13.6 is the highest rate ever recorded for 15–24-year-olds in the United States, and that peak and subsequent leveling off and slight decrease in rates correspond to the leveling off and beginning of the decrease of the young population.

There are important psychiatric and public health implications in this model. According to current population projections, the decrease in the number and proportion of 15–24-year-olds will be ending in the mid-1990s, and another increase in 15–24-year-olds will begin at that time (35). Thus, the population model would suggest that the government, schools, employers, health services, etc., should be ready to respond to that increase with more psychiatric services, counselors, jobs, and high school and college facilities. A preventive response would thus be created, rather than an “after-the-fact,” reactive model.

With respect to the older age groups, our data lead to the prediction that if the proportion of older people increased, their suicide rate would decrease—although probably not to the lower rates seen among the young because of the age effect, i.e., the tendency of suicide rates to increase with age (age effects involve changes in age-specific rates of mortality or illness over the life span of the individual [27]). Again, important psychiatric and public health implications would result from these findings should the predictions hold up. For example, older people would be at particularly increasing risk of suicide if their proportions decreased, and health agencies, government, and business could respond with very specific services in mental and physical health, employment, and housing.

Implications for Future Research

Three areas of future research appear particularly important with respect to violent deaths, their potential for prediction, and population changes. First, it is critical that the epidemiologic data be increasingly accurate, both in terms of mortality data (local and national) and the population bases from which mortality rates are derived. Second, prospective studies are needed to specifically test the hypotheses regarding the potential for the prediction of violent death rates on the basis of population shifts. Mathematical models need to be developed that could predict violent death rates on the basis of projections of the future population. Finally, at least two types of cross-cultural studies of violent death would be useful: long-term cross-cultural comparisons of suicide and homicide and cross-cultural studies that examine suicide and homicide with specific reference to evaluation of the predictive and preventive aspects of the population model.

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The Clinical Significance of Command Hallucinations

David Hellerstein, M.D., William Frosch, M.D., and Harold W. Koenigsberg, M.D.

Patients with command hallucinations (voices ordering particular acts, often violent or destructive ones) are commonly assumed to be at high risk for dangerous behavior. The authors reviewed 789 consecutive inpatient admissions. Of 151 patients with auditory hallucinations, 58 (38.4%) heard commands. The presence of auditory hallucinations was significantly associated with diagnosis, demographic variables, and use of maximal observation and seclusion. However, patients with command hallucinations were not significantly different from patients without commands on demographic and behavioral variables, including suicidal ideation or behavior and assaultiveness. These findings suggest that command hallucinations alone may not imply greater risk for acute, life-threatening behavior.

(Am J Psychiatry 1987; 144:219–221)

Clinicians often use the presence of command hallucinations in prognosticating and making clinical decisions about psychotic patients. Command hallucinations are auditory hallucinations that instruct

a patient to act in a certain manner—ranging from making a gesture or grimace to committing suicidal or homicidal acts.

In clinical psychiatric practice the presence of command hallucinations has been used as a justification for emergency hospitalization of psychotic patients. A patient with command suicidal or homicidal hallucinations is believed to be at great risk for committing violent acts, yet there is no clear evidence that such a risk exists.

Command hallucinations have been described in the literature over many years (1–3). The recent psychiatric literature is divided on the issue of their clinical significance. Yesavage (4) has stated that the presence of command hallucinations is associated with “danger-related events” on inpatient units. However, Goodwin et al. (5) found that patients generally ignore hallucinatory commands, and Breier and Astrachan (6), in a study of 20 schizophrenic patients who committed suicide, found that no patients had reported commands. Jansson (7) reported that six of 15 patients with “imperative hallucinations” fell into the worst-outcome category but stated that a poor prognosis was not inevitable. To our knowledge, no large study has specifically tried to determine the population in which command hallucinations occur, whether that population is at a high risk for violent acts on an acute basis, or whether there is a worse long-term prognosis.

METHOD

We reviewed a previously compiled computerized data file on 789 sequentially admitted inpatients at Payne Whitney Clinic in 1979 and 1980. A total of 175 variables had been previously coded by a trained

Presented at a new research session at the 138th annual meeting of the American Psychiatric Association, Dallas, May 18–24, 1985. Received Nov. 19, 1985; revised June 2, 1986; accepted July 16, 1986. From the Department of Psychiatry, Payne Whitney Clinic, Cornell University Medical Center, New York. Address reprint requests to Dr. Hellerstein, Adult Psychiatric Outpatient Service, Beth Israel Medical Center, 10 Nathan D. Perlman Place, New York, NY 10003.

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rater from admission and discharge summaries, including demographic data; past psychiatric history; suicidal and assaultive acts in the 2 weeks before admission; mental status at admission; admission and discharge diagnoses; length of stay; and use of restraints, seclusion, and maximal observation in the hospital.

Of the 789 patients, 180 had had hallucinations within 2 weeks before admission. A total of 151 had had auditory hallucinations; their charts were reviewed by two psychiatrists for the presence or absence of command hallucinations.

Frequency tables were printed out for 20 variables for 1) the group without auditory hallucinations (N=638), 2) the group with auditory hallucinations (N=151), 3) the group with noncommand auditory hallucinations (N=93), and 4) the group with command auditory hallucinations (N=58). The following variables were compared between groups 1 and 2 and between groups 3 and 4: age; sex; race; marital status; *DSM-II* axis I and II diagnosis; suicidal ideation and acts; assaultive acts; length of hospitalization; and use of maximal observation, restraints, and seclusion. The same variables were compared among the subsample of schizophrenic patients (N=159).

RESULTS

We report results as comparisons 1) between patients with and patients without auditory hallucinations and 2) of patients with auditory hallucinations, between those with commands and those without commands.

The prevalence of auditory hallucinations in the inpatient population was 19.1% (151 of 789 patients). The prevalence of command auditory hallucinations was 7.35% (58 of 789 patients). A total of 38.4% of the patients with auditory hallucinations reported commands. Of the 159 patients with a diagnosis of schizophrenia, 64 (40.3%) had auditory hallucinations, and 29 of these (18.2%) had command hallucinations. Of the 167 patients with a diagnosis of affective disorder, 22 (13.2%) had auditory hallucinations, and seven of these (4.2%) had command hallucinations. Among the 165 patients with an axis II diagnosis, 19 (11.5%) had auditory hallucinations, and five of these (3.0%), all diagnosed as having borderline personality disorder, had command hallucinations.

Patients with auditory hallucinations were significantly more likely to be diagnosed as schizophrenic than patients without auditory hallucinations (42.4%, N=64, versus 14.9%, N=95) and less likely to be diagnosed as affectively ill (14.6%, N=22, versus 22.7%, N=145; $\chi^2=72.2$, $df=4$, $p<.001$). Hallucinating patients had significantly fewer axis II diagnoses than nonhallucinating patients (12.6%, N=19, versus 22.9%, N=146; $\chi^2=8.3$, $df=1$, $p<.005$).

There was no significant difference in diagnosis between the two subgroups with hallucinations, either on axis I or axis II. Of the patients with command

hallucinations, 50% (N=29) were given a diagnosis of schizophrenia; 10.3% (N=6), atypical psychosis; 12.1% (N=7), affective disorder; 3.4% (N=2), alcohol abuse; and 24.1% (N=14), other diagnoses.

As might be expected, there was a significant difference between the groups with and without auditory hallucinations on a number of demographic variables. Patients with hallucinations were significantly younger (age less than 31 years) (61.3%, N=93, versus 42.3%, N=270; $\chi^2=16.8$, $df=1$, $p<.001$), were more likely to be single (63.3%, N=96, versus 48.9%, N=312; $\chi^2=11.3$, $df=3$, $p<.01$), and were more likely to be black (28.9%, N=44, versus 19.9%, N=126; $\chi^2=5.2$, $df=1$, $p<.02$).

There were no significant associations between age, sex, race, or marital status and the presence of command hallucinations.

Analysis of the content of command hallucinations in the 58 patients showed that 51.7% were of suicide; 5.2%, homicide; 12.1%, nonlethal injury of self or others; and 13.8%, nonviolent acts. The content was unspecified in 17.2%.

There was no difference in medication dose at discharge between the patients with noncommand and command hallucinations (659 mg/day versus 651 mg/day of chlorpromazine equivalents).

Hallucinating patients were as likely to have suicidal ideation as nonhallucinating patients, but they had a nonsignificant trend toward less acting on suicidal impulses (11.9%, N=18, versus 17.6%, N=112; $\chi^2=2.4$, $df=1$, $p<.12$). Patients with command hallucinations had a trend toward more suicidal ideas than patients with noncommand hallucinations (51.7%, N=30, versus 36.6%, N=34; $\chi^2=2.8$, $df=1$, $p<.09$), but there was no difference in suicidal acts (13.8%, N=8, versus 10.8%, N=10; $\chi^2=.09$, $df=1$, n.s.).

There was no significant difference in assaultive acts between the groups with and without auditory hallucinations or between the groups with and without command hallucinations.

There were several significant differences between the hospital stays of hallucinating and nonhallucinating patients. Hallucinating patients had significantly fewer brief (less than 15-day) hospitalizations than nonhallucinating patients (17.8%, N=27, versus 35.1%, N=221; $\chi^2=15.9$, $df=1$, $p<.001$); they did not, however, have longer hospitalizations. Hallucinating patients were significantly more likely to be put in seclusion rooms than nonhallucinating patients (23.2%, N=35, versus 13.9%, N=89; $\chi^2=7.2$, $df=1$, $p<.007$). Maximal observation (one-to-one staff assignment) was used significantly more often among hallucinating patients (25.8%, N=39, versus 17.4%, N=111; $\chi^2=5.1$, $df=1$, $p<.024$). Physical restraints were used equally infrequently with hallucinating and nonhallucinating patients (4%, N=6, and 3%, N=19).

The same variables were measured for patients with command and noncommand hallucinations. There was no association between the presence of command

hallucinations and length of hospitalization. There were no significant differences between patients with command and noncommand hallucinations in use of seclusion (17.2%, $N=10$, versus 26.9%, $N=25$; $\chi^2=1.4$, $df=1$, n.s.) and maximal observation (31.0%, $N=18$, versus 22.6%, $N=21$; $\chi^2=0.93$, $df=1$, n.s.). Physical restraints were used equally infrequently in patients with command and noncommand hallucinations (3.4%, $N=2$, and 4.3%, $N=4$).

Data were analyzed to determine whether there might be significant differences for the schizophrenic patients, the largest group of hallucinating patients. Of the 159 schizophrenic patients, 64 had auditory hallucinations and 29 had command hallucinations. Patients with command hallucinations had significantly more short (less than 15-day) hospitalizations than patients with noncommand hallucinations (34.5%, $N=10$, versus 8.6%, $N=3$; not just, $\chi^2=4.7$, $df=1$, $p<.04$). There were no other significant differences between the two groups of hallucinating schizophrenic patients.

DISCUSSION

Many psychiatric patients with auditory hallucinations (in this study, 38.4%) hear commands to behave in a particular manner, often violently or self-destructively. Traditionally, command hallucinations have been thought to indicate a high risk for dangerous behavior and to necessitate emergency hospitalization and close observation. Although clinicians occasionally see psychotic patients who have acted destructively on the basis of auditory commands, there has been no convincing evidence that such patients are statistically at a high risk for dangerous behavior.

The purpose of this study was to look at a large population of patients with command hallucinations and to evaluate this perception of high risk. While the study was potentially limited by its retrospective nature and by possible coding errors, the presence of many strong associations for the hallucinating versus nonhallucinating populations confirms that data were coded properly. Our results are only preliminary and need replication and extension in other settings, including outpatient departments and emergency rooms, and with high-risk populations, such as forensic psychiatric patients.

Our results raise certain questions regarding the

traditional beliefs about command hallucinations. While the previous clinical impression of the diagnostic nonspecificity of command hallucinations appears to be correct, the short-term prognostic significance of command hallucinations has not been confirmed. It is possible that the use of command hallucinations as a risk variable belongs to clinical folklore, not fact.

If there is an association between command hallucinations and violent behavior or other prognostic measures, it may well not exist for the sample of patients with command hallucinations as a whole. It appears that most such patients ignore the commands. However, there may be subgroups of patients who are at risk. Patients who have acted violently in the past in response to command hallucinations or patients with previous impulsive or violent behavior may be at high risk for violent behavior if command hallucinations occur. Patients who currently act violently in response to commands usually need hospitalization and close observation. Perhaps patients who hear repetitive commands with an intrusive, peremptory quality or for an extended period of time are at a high risk. However, it is not clear whether it is the command hallucinations that are most significant or merely the presence of *any* disturbing acute psychotic symptoms (including delusions, bizarre perceptions, and hallucinations of any kind). Similarly, psychotic patients presenting for evaluation after a suicide attempt or an assaultive act may be at risk for violent behavior because of their tendency to act violently, rather than because of the presence of command hallucinations.

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Auditory Hallucinations and Subvocal Speech in Schizophrenic Patients

Peter A. Bick, M.D., and Marcel Kinsbourne, M.D.

Fourteen of 18 hallucinating schizophrenic patients reported that the voices they heard went away when they undertook a maneuver that precluded subvocalization. The same applied to 18 of 21 normal subjects who hallucinated under the influence of hypnotic suggestion. Control maneuvers had no such effect. The authors suggest that auditory hallucinations may be projections of schizophrenic patients' verbal thoughts, subvocalized due to deficient cerebral cortical inhibition.

(Am J Psychiatry 1987; 144:222-225)

Hallucinations have variously been regarded as 1) an expression of excess (e.g., disinhibited) brain activity or 2) products of adaptive behavior, either searching for organization in a chaotic array or motivated by dynamic imperatives. Each approach derives support from a different domain of hallucinatory experience: drug, seizure, and electrical stimulation effects; perceptual isolation; and the content of hallucinations of psychotic patients. They are not mutually exclusive. In particular, thought-disordered content could be superimposed on either primary or compensatory brain-based phenomena.

We have examined auditory hallucinations with respect to the recurrent claim that they are accompanied by subvocalization. Subvocalization could either accompany ("shadow") hallucinated voices or mediate (generate) them.

Following Hansen and Lehmann's suggestion (1) that covert oral behavior occurs during thinking, Perky (2) demonstrated subtle laryngeal movements in 84% of 155 subjects asked to form memory images but in only 9% of 214 subjects asked to form abstract images. The activity of vocal musculature increases even when normal control subjects merely concentrate (3-5). Subvocalizing during reading decreases reading speed but improves comprehension (6). Objective evidence of subvocalization during silent reading tasks

was first provided by Faaborg-Anderson and Edfeldt (7). Using an electromyogram (EMG), they found increased laryngeal muscle activity in five subjects reading unfamiliar foreign prose (as compared to their native language). Thus, when words are difficult to phonemically encode, subvocalization increases.

McGuigan et al. (8, 9) demonstrated that when reading in distracting conditions, children and poor readers exhibit large-amplitude laryngeal EMG activity; the amplitude is inversely related to reading speed (8-10). McGuigan hypothesized that laryngeal movements code the words being read (11).

In 1897 Parish (cited by Gould [12]) conjectured that patients who report hallucinations concurrently generate automatic speech. In 1914 Seglas (13) termed this phenomenon "verbal pseudohallucination." La Gache in 1935 (14) made the causal inference that verbal hallucinations are a distortion of self-produced speech. Several reports endorsed this idea (15-17), and Gould (12, 17, 18) was the first to support it with objective data. He found a close correspondence between the content of subvocal speech, recorded with a microphone close to the mouth, and the reported content of hallucinations. There also was a surge of EMG activity recorded from the lower lip each time the patient signaled a hallucination. Eighty percent of 56 schizophrenic patients had increased chin EMG activity while hallucinating, whereas 10% of 33 nonhallucinating control subjects had such EMG activity in similar test conditions (18). However, although Roberts et al. (19) confirmed increased subvocal activity in hallucinating compared to nonhallucinating schizophrenic patients, they found no specific relationship between increased subvocalization and the actual period during which the hallucinations occurred.

Lindsley (20) recorded vocalizations by a voice key and a hidden microphone set to filter out nonspeech wavelengths. He thought that a high frequency of vocalization was an index of hallucinations. He was able to provoke vocal activity by auditory stimulation, to the extent that it resembled the human voice. He took the vocalization to represent the patients' response to their voices (or extraneous sounds). McGuigan (21) reported increased chin EMG and breathing amplitude two seconds before the report by button press of hallucination. In two instances, whippers picked up with a microphone near the patient's

Received May 13, 1985; revised July 10, 1986; accepted Aug. 18, 1986. From Harvard Medical School, Boston; and the Eunice Kennedy Shriver Center. Address reprint requests to Dr. Kinsbourne, Division of Behavioral Neurology, Eunice Kennedy Shriver Center, 200 Trapelo Rd., Waltham, MA 02254.

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lips resembled the later reported content of the hallucinations. This finding was replicated with nine schizophrenic subjects (22). Amplified subvocalizations from a hallucinating patient were relayed to three independent raters (23), who rated 108 of 142 segments as resembling the content of the hallucinations reported by the patient. These included orders in the third person, which are considered to be typical of schizophrenic hallucinations.

Inouye and Shimizu (22) recorded, by needle electrodes, activity from four speech muscles in nine schizophrenic patients. The patients depressed a switch whenever they experienced a hallucination. Significantly more vocal activity was observed at that time than when subjects were asked to depress the switch randomly. In addition, vocal EMG was transduced into sound in two cases. Patients confirmed that the onset of the sound coincided with the onset of their hallucinations.

These findings were all correlative (but see reference 23), and the correlations were not always exact (20). Indeed, Lindsley (20) took the vocalizations to be the patient's *response* to the hallucination. The data thus far do not prove that the voices are actually the patients' own speech sounds.

We carried out a pilot study of eight schizophrenic patients who complained of voices. Each patient was asked to perform two tasks, one of which (holding the mouth wide open) has been shown to prevent subvocalization in normal subjects (Nazarova, cited by Luria [24]; Bond and Tinker [25]). The other, a control task, was to clench the fists and squeeze tightly. Six of the eight patients reported that the voices disappeared when they held their mouths open but not when they clenched their fists. In view of these results, a controlled experiment was devised. In it, the interviewer was unaware of the hypothesis. In case a patient might assume that a facial movement would affect voices more than the manual control task, a facial exercise that does not interfere with subvocalization was used as an additional control.

EXPERIMENT 1

Method

The subjects were 18 psychiatric inpatients who met *DSM-III* criteria for schizophrenia; they consisted of 11 men and seven women 21–63 years old. Most ($N=11$) had been inpatients for over 3 months, and the remainder were seen in an acute admission ward. All were taking psychoactive drugs. They all described hearing voices that spoke to them, gave them commands, or commented on their behavior. All patients who admitted to hearing voices at the time of the initial interview were included in the study. The 11 chronic patients said that they had been hearing voices almost every day for 2–33 years.

The experimenter made the following statement to

the patients: "I am going to ask you to do some exercises and I want you to tell me after each exercise if your voices got worse, stayed the same, or went away." In a random order, counterbalanced across subjects, the experimenter asked the patients to 1) close their eyes tight, 2) open their mouths wide, and 3) make fists and squeeze tight for 1 full minute and then to comment on the status of the voices they heard. The experimenter rated each reply as indicating an increase, a decrease, or no change in the voices.

Results

The mouth-opening maneuver abolished hallucinations in most subjects, but the fist and eye maneuvers did not. No one reported an intensification of voices (table 1).

The patients complied readily but seemed indifferent to the fact that they could abolish the voices by a simple movement. Patients who had characterized the voices they heard as burdensome or terrifying expressed no relief that they could control them. One patient who reported hearing continuously harassing voices was reinterviewed 1 week later. Asked if she had used the mouth-opening maneuver when the voices became intolerable, she said that she had not and expressed no interest in doing so.

Discussion

The finding that obstructing subvocalization suppresses auditory hallucinations clarifies the mechanism by which these experiences are generated. The previously reported correlation between voices and subvocal activity did not identify cause and effect. The patient could have been repeating (shadowing) what he or she heard (20). But were that so, the patient could not have inhibited the perceptual experience by otherwise engaging his or her vocal apparatus. We therefore infer the following sequence of events: The patient subvocalizes, listens to his or her covert speech, and attributes it to another.

Such dissociated behavior is not unprecedented. The victim of possession regards his or her vocal apparatus as under the control of another—for instance, a demon. When people speak in tongues, they sometimes attribute the speech to some hypothetical individual (26). Hypnosis is another dissociated state (27). The second experiment investigated whether hypnotically suggested voices are also generated subvocally.

EXPERIMENT 2

Method

Twenty-one volunteer college students, 11 men and 10 women 21–30 years old, were told that while hypnotized, they would be given some harmless suggestions to follow. During hypnosis it was suggested

TABLE 1. Ability of Motor Maneuvers to Abolish Hallucinations in Schizophrenic Patients and Hypnotized Normal Subjects

Group	Sex	Maneuver-Abolished Hallucination		
		Fist	Eye	Mouth
Patients ^a				
1	M			Yes
2	M			Yes
3	F			Yes
4	F			
5	M	Yes	Yes	Yes
6	M			Yes
7	M			
8	F			Yes
9	M			Yes
10	M			Yes
11	F			
12	F			
13	M			
14	F			Yes
15	M			Yes
16	M			Yes
17	M			Yes
18	F		Yes	Yes
Normal subjects ^b				
1	F			Yes
2	M			Yes
3	M			Yes
4	M			
5	F			Yes
6	F	Yes	Yes	Yes
7	M			Yes
8	M			Yes
9	F			Yes
10	M	Yes	Yes	Yes
11	F			Yes
12	M			Yes
13	M			
14	F			Yes
15	F			Yes
16	M			
17	M			Yes
18	F			Yes
19	F			Yes
20	F			Yes
21	M			Yes

^aFor schizophrenic patients, there was a significant difference among the maneuvers ($\chi^2=26.95$, $df=2$, $p<.01$). There was also a significant difference between mouth maneuvers and fist and eye maneuvers ($\chi^2=26.38$, $df=1$, $p<.001$).

^bFor normal subjects, there was a significant difference among the maneuvers ($\chi^2=35.77$, $df=2$, $p<.01$). There was also a significant difference between mouth maneuvers and fist and eye maneuvers ($\chi^2=34.52$, $df=1$, $p<.001$).

that they hear voices. Fourteen other subjects were rejected after they failed either to be hypnotized or to hear voices. Everyone who initially acknowledged hearing voices was included.

Subjects were instructed as in experiment 1.

Results

The mouth-opening maneuver abolished hallucinations in a majority of subjects significantly more often than did fist and eye maneuvers (table 1).

These normal subjects typically heard a mixture of men's and women's voices in a low-volume murmur-

ing that was difficult to understand. They reacted by expressing amusement or bewilderment. They shared the schizophrenic patients' indifference to the effect of mouth opening in abolishing the voices and were untroubled when the voices returned after the mouth-opening maneuver ended.

Discussion

When normal subjects hear voices under hypnotic suggestion, they self-generate the sounds. This finding demonstrates the sweeping generality of the subvocal genesis of hallucinated voices. It aligns the schizophrenic patient's experience with behavior to which normal subjects may "unconsciously" resort.

GENERAL DISCUSSION

We found that mouth opening selectively dispels hallucinated voices. Thus, self-produced subvocalizations are experienced as voices. The results confirm that subvocalization accompanies auditory hallucinations in schizophrenic patients. However, the previous literature included no specific or controlled manipulation of this phenomenon. Nonspecific distraction can account for reportedly successful manipulations, as when two patients with chronic hallucinations treated themselves, one by wearing stereo headphones and the other by watching television (28, 29). Distraction could also explain the alleged success of other coping devices used by patients (30), including jogging, singing, dancing, reading, listening to the radio or television, thinking of other things, and naming (31) and speaking (32-35) to another person. Thus, until now, the alternative hypothesis could not be excluded that schizophrenic patients shadow, in whispers, voices that they hear (21). From the present data we can draw a stronger inference. Schizophrenic patients actually generate the voices; they do not merely shadow them. The voices' messages reflect the patients' disordered thought processes, projected on other, imagined, speakers. The projection process would be held responsible for grammatical differences between patients' thoughts and the corresponding hallucinations and for the report of tonality of voice that is different from the patient's own.

Another novel finding is that during hypnotic suggestion, normal subjects similarly set up the suggested voices. Given that this mechanism is so general, one wonders whether subvocalization also mediates the experience of voices when it is generated by temporal lobe lesions (36, 37) or direct electrical stimulation of specific areas of the exposed temporal (38, 39) or frontal (40, case 3) cerebral cortex.

Although hallucinating patients may be taught how to control their voices by simple maneuvers, caution should be exercised before this finding is used for purposes of treatment, lest one thereby deprive the patient of a helpful compensatory device. For instance,

if hallucinations help the patient cope with disorganized sensory input, removing the hallucinations in this way, or by aversive conditioning (30, 32, 35, 41–43), might expose the patient to a more dissonant state. An adaptive function of hallucinated voices may explain the patients' disinterest in the revelation that they themselves could control the production of the voices. If the subvocalizations represent the patients' verbal thoughts, disinhibited into vocal activity, treating the voices would be therapy at an inappropriate level. Instead, the thought processes themselves require attention. If, say by some chemical means, it became possible to strengthen patients' inhibitory processes, then it would become apparent whether patients benefit (because the aversive voices would be gone) or actually deteriorate (because they would have been deprived of a way to project troubling thoughts, used as a coping device).

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Depression in Chinese Medical Inpatients

Lingling Yang, M.D., Chenyeh Zuo, M.D.,
Lingyan Su, M.D., and Merrill T. Eaton, M.D.

The authors studied depressive symptoms among 251 Chinese medical inpatients through the use of the Beck Depression Inventory. Assessment of 100 healthy Chinese volunteers validated the use of American score norms for Chinese subjects. A total of 47.8% of the 251 medical inpatients (N=120) met the Beck scale criterion for depression. Beck scale scores varied with the occupation of patients and the severity of medical illness but did not vary with sex, age, marital status, duration of hospitalization, or medical diagnosis.

(Am J Psychiatry 1987; 144:226-228)

It is not uncommon for medical patients to manifest depressive symptoms. Intervention in these secondary depressions is among the major concerns of consultation-liaison psychiatry. Since psychiatric consultation in China follows a traditional patient-centered pattern (1), studies of psychological reactions to physical illness in the Chinese population are potentially useful. They can help Chinese mental health professionals, and perhaps those of some other countries, to recognize the need for consultation-liaison services. Where such services are already well developed, comparative findings may be of interest.

In this study the Beck Depression Inventory was administered to 251 Chinese medical inpatients to evaluate their depressive symptoms. To our knowledge this is the first investigation of this topic in the People's Republic of China.

METHOD

The study group consisted of 251 inpatients consecutively admitted to the medical wards of the Second Affiliated Hospital of Hunan Medical College in a 2-month period in 1983. This group represented 74% of all patients admitted to medical wards during that

time. The remaining 26% of the patients (N=87) were not included because they were too ill to participate in the study (N=40), refused to be assessed (N=36), or had a definite diagnosis of psychiatric disorder (N=11). The demographic characteristics of the 251 patients are shown in table 1.

The primary medical diagnoses of the 251 patients were as follows: respiratory diseases (N=42), cardiovascular diseases (N=45), gastrointestinal diseases (N=41), renal diseases (N=26), endocrine diseases (N=34), hematologic diseases excluding leukemia (N=20), and carcinoma and leukemia (N=23). Twenty patients had other miscellaneous diagnoses.

To make sure that American norms for Beck scale scores were applicable to Chinese subjects, 100 healthy volunteers were tested. In this control group there were 40 medical students, 35 psychiatric staff members, and 25 workers. None of them presented evidence of current or past psychiatric disorder or evidence of active physical illness. There were 57 men and 43 women; their age ranged from 20 to 52 years (mean \pm SD=27.62 \pm 8.03 years). Fifty-nine subjects were married and 41 were single. Another control group consisted of 20 patients with major depressive disorders. There were 14 women and six men; their age ranged from 21 to 66 years (mean \pm SD=42.2 \pm 12 years). All but two were married.

The Beck Depression Inventory is a self-rating scale for assessing depressive symptoms. Its validity in Americans has been documented (2). For this study the Beck scale was translated into Chinese and then translated back into English by bilingual psychiatrists. The Beck scale contains 21 items. The score on each item ranges from 0 to 3 depending on severity of illness; the overall score ranges from 0 to 62. According to Beck in a communication to Schwab (3), those with a total score of 0 to 13 are nondepressed, those scoring 14-24 are mildly to moderately depressed, and those scoring 25 and above are highly depressed.

Of the 251 medical inpatients, 147 were assessed in the first 1-3 days after admission, and the remaining 104 were assessed during the 4th to 176th day of hospitalization (mean \pm SD=29.4 \pm 33.9 days). In addition to the Beck rating, one of us (C.Z.) reviewed the medical records of all 251 patients and interviewed patients scoring 14 or above. Those with definite diagnoses of psychiatric disorders were excluded from the research group. Hence, the depressive symptoms

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TABLE 1. Demographic Characteristics of 251 Chinese Medical Inpatients

Characteristic	Number of Patients
Sex	
Male	152
Female	99
Age (years)	
10-19	27
20-29	40
30-39	49
40-49	56
50-59	45
60+	34
Marital status	
Married	172
Single	45
Widowed	5
Data not available	29
Occupation	
Professional/administrator	95
Worker	85
Farmer	47
Student	15
Data not available	9

reported in this study reflect more the demoralization associated with disease than clinical depressive illnesses as such.

Diagnoses of the 20 control patients with major depressive disorders were made by one of us (L.S.) using the Research Diagnostic Criteria.

RESULTS

The Beck scale scores of the 251 medical inpatients ranged from 0 to 38. A total of 131 inpatients (52.2%) scored 0-13; 120 (47.8%) scored 14 and above (mean \pm SD=21.63 \pm 6.41). The Beck scale scores of the 100 healthy subjects ranged from 0 to 15 (mean \pm SD=6.68 \pm 4.18). Ninety-six of these 100 subjects scored 0-13, and four subjects scored 15. The Beck scale scores of the 20 patients with major depression ranged from 20 to 53 (mean \pm SD=34.95 \pm 9.17). Seventeen of these 20 patients scored 25 or above; the other three patients scored 20, 22, and 23. There was a significant difference between the mean Beck scale score of the 120 medical inpatients scoring 14 and above and the mean score of the 20 patients with major depression ($t=8.02$, $df=138$, $p<.001$).

Of the 251 medical inpatients, 152 were men. Eighty-four (55.3%) of these had Beck scores within the range of 0 to 13, 53 (34.9%) had scores of 14 to 24, and 15 (9.8%) scored 25 or above. Ninety-nine patients were women. Forty-seven (47.5%) of them had Beck scores within the range of 0 to 13, 33 (33.3%) had scores in the range of 14 to 24, and 19 (19.2%) had scores of 25 or above. There was no significant difference between the Beck scores of men and women ($\chi^2=4.18$, $df=2$, $n.s.$).

The 27 medical inpatients in the 0-19-years age group had a mean Beck score of 15.52, the 40 patients

TABLE 2. Relationship of Beck Depression Scores to Occupation and Severity of Illness Among Chinese Medical Inpatients

Variable	Mean Beck Score
Occupation (N=242) ^a	
Professional/administrator (N=95)	11.73
Worker (N=85) ^b	15.89
Farmer (N=47) ^c	17.72
Student (N=15)	11.33
Severity (N=251) ^d	
Mild (N=105)	12.04
Moderate (N=103)	14.90
Severe (N=43) ^e	18.50

^aSignificant differences between groups ($F=7.27$, $df=3$, 238, $p<.01$).

^bSignificant difference between workers and professionals/administrators ($Q=3.2$, $p<.05$) and workers and students ($Q=3.51$, $p<.05$).

^cSignificant difference between farmers and professionals/administrators ($Q=4.61$, $p<.01$) and farmers and students ($Q=4.92$, $p<.01$).

^dSignificant differences between groups ($F=9.27$, $df=2$, 248, $p<.01$).

^eSignificant difference between severely and mildly ill patients ($Q=5.57$, $p<.01$) and severely and moderately ill patients ($Q=3.1$, $p<.05$).

20-29 years old had a mean score of 14.25, the 49 patients 30-39 years old had a mean score of 15.59, the 56 patients 40-49 years old had a mean score of 13.61, the 45 patients 50-59 had a mean score of 13.12, and the 34 patients 60 or above had a score of 14.79. No significant differences were found among the age groups ($F=0.58$, $df=5$, 245, $n.s.$).

There were no significant differences between married and single subjects ($\chi^2=0.55$, $df=4$, $n.s.$).

The Beck scores of different occupational groups are shown in table 2. The mean scores of workers and farmers were significantly higher than those of administrators, professionals, and students.

There were no significant differences among medical diagnoses classified by system or when malignant disorders were compared with other illnesses. Among these 251 medical inpatients, 76 had psychosomatic illness; their mean Beck score was 15.67. Eighteen patients knew they had incurable diseases; their mean score was 13.83. The mean score of the other 153 patients was 13.27. No significant differences were found among Beck scores of these three groups ($F=1.88$, $df=2$, 244, $n.s.$). In addition to these three groups, there were four patients, too few for statistical comparison, with severe pain. The Beck scores for these patients were 24, 25, 29, and 35, respectively (average=28.25).

Patients were classified by severity of medical illness. The mean Beck score of severely ill patients was 18.5, while those of moderately and mildly ill patients were 14.9 and 12.04, respectively. These differences were statistically significant (table 2).

There was no significant difference in the scores of patients assessed in the first 3 days of hospitalization and those tested between the 4th and 21st day or those after the 22nd day.

DISCUSSION

There were two reasons for choosing the Beck Depression Inventory as the instrument to be used in this study. One was that the content of the Beck scale is easily comprehensible to Chinese subjects. The other was that the Beck scale is a self-rating scale for assessing depressive symptoms without reference to diagnosis.

The mean \pm SD Beck score of 100 healthy Chinese subjects was 6.68 ± 4.18 . Ninety-six of these subjects scored within the nondepressed range of Beck's score norm, while the other four subjects scored only 1 point higher than the cutoff point. It seems appropriate with Chinese subjects to follow Beck's original use of 14 as the cutoff point discriminating depression and nondepression.

The medical records of all subjects were reviewed, and those patients scoring 14 or above were interviewed. Those with specific psychiatric disorders, current or past, were excluded. Accordingly, the depressive symptoms presented by the remaining 120 medical inpatients were emotional responses and/or psychophysiological reactions to physical illness.

It has been reported (4, 5) that the prevalence of depressive disorders in the Chinese population is relatively low. In recent years this has been questioned. The previously reported lower rate of depression in China seems to be the reflection of differences in diagnostic criteria rather than differences in prevalence per se (6-8). The use of the diagnosis of neurasthenia for some patients with depressive symptoms in China may play an important role in this apparent discrepancy. In 1982 Kleinman (6) reported a study of 100 Chinese patients diagnosed by Chinese psychiatrists as having neurasthenia. He found that 87 of these 100 patients met the *DMS-III* criteria for major depressive disorder. In 1986 Zuo (9) reported observations in the United States. He found that many cases of major depressive disorder without melancholia and without psychotic features as diagnosed by American psychiatrists fitted the criteria for neurasthenia used by Chinese psychiatrists (10).

There have been several reports of the use of the Beck scale to study depression in medical inpatients. In 1967 Schwab et al. (11), using the cutoff point of 14 on the Beck scale, found that 22% of their 153 medical inpatients were depressed. In 1975 Moffic and Paykel (12) carried out a similar study of 150 medical inpatients and found that 28.7% of them were depressed. The higher frequency of depression in our medical inpatient group may be attributed to the severity, complexity, and longer duration of the medical illness. The current public health service in the People's Re-

public of China uses the "three-level system." Patients are first seen in primary care services. Difficult cases will be referred to the municipal or prefectural hospitals and, if necessary, will be further referred to the provincial-level services such as our hospital. In general, patients seen in our hospital are either those with more severe or complicated illness or those with illness of protracted course. These factors would be expected to increase the Beck scale scores of the patients.

The Beck scores of our medical inpatient group were related both to the occupation of patients and the severity of medical illness and were not related to such variables as sex, age, marital status, duration of hospitalization, and medical diagnostic category. These findings are consistent with those of other studies (3, 11, 12).

Our study indicates that depressive symptoms may be common phenomena in Chinese medical patients. We believe this finding warrants further investigation. A better understanding of the impact of illness on the emotional state of hospitalized patients can help us improve the hospital milieu to better meet the needs of our patients. If explanations can be found for differences between cultures, knowledge of the reasons for these differences may contribute to improved patient care.

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Blunted Aldosterone and ACTH Release After Human CRH Administration in Depressed Patients

Florian Holsboer, M.D., Ph.D., Armand Gerken, M.D., Günther K. Stalla, M.D.,
and Otto A. Müller, M.D.

The authors measured pituitary adrenocortical responses to human corticotropin-releasing hormone (CRH) in 10 patients with a major depressive episode and 10 matched control subjects. Depressed patients had a significantly lower aldosterone and ACTH release, but cortisol and corticosterone responses were not different between groups.
(Am J Psychiatry 1987; 144:229-231)

Recent sequencing and synthesis of the human corticotropin-releasing hormone (CRH) have provided a new tool to study the pathophysiology of exaggerated pituitary adrenocortical activity in depression. Few recent studies using either human CRH or its ovine analogue have supported the idea that pituitary and adrenocortical cell function is intact in depression. Elevated cortisol secretion in depressed patients has been associated with significant blunting of the net ACTH response after ovine or human CRH administration (1, 2). The heterologous ovine CRH was found to stimulate not only cortisol and corticosterone but also aldosterone in normal control subjects (3). Although several previous studies surmised that regulation of aldosterone is impaired in depression (4-6), data on aldosterone responses to human CRH in

patients with depression are lacking. The present study was designed to compare ACTH with glucocorticoid and mineralocorticoid response after human CRH administration in patients with depression and normal control subjects. In addition to using aldosterone and cortisol, we also used corticosterone because it has recently been shown that this minor glucocorticoid is a more sensitive measure than cortisol of pituitary adrenocortical responsiveness after ovine CRH challenge in depressed patients (7).

METHOD

Ten psychiatric inpatients (five men and five women) suffering from a major depressive episode according to *DSM-III* entered the study. Their mean \pm SD age was 48.8 ± 7 years (range=40-62), and all had been free from any medication for at least 14 days. Ten normal control subjects (five men and five women) participated on a paid, voluntary basis. Their mean age was 43 ± 8 years (range=35-62). The depressed patients and control subjects were carefully examined for medical factors that could invalidate study results. These examinations included determination of electrolytes in plasma and 24-hour urine collections on 2 consecutive days, confirmation of present normotension and absence of past history or family history of hypertension, investigation of hormonal status (including thyroid hormones), and exclusion of present or prior abuse of nicotine or caffeine-containing beverages. If patients or control subjects had been exposed to drugs that might interfere with mineralocorticoid homeostasis, they were not included.

All subjects gave informed consent to participate. They rested in a supine position in a bed for 7 hours and received an electrolyte-balanced diet at 8:00 a.m. and 12:30 p.m. Several hours before the first blood

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TABLE 1. Pituitary Adrenocortical Response to a 100- μ g Bolus Injection of Human CRH in 10 Patients With *DSM-III* Recurrent Major Depressive Episode and in Normal Control Subjects

Subject	Age (years)	Sex	Additional Diagnostic Features	Hamilton Score	ACTH (pg/ml/min)	Aldosterone (pg/ml/min)	Corticosterone (ng/ml/min)	Cortisol (ng/ml/min)
Depressed								
1	57	F	Mood-congruent psychotic with melancholia	30	4,845	1,395	480	12,930
2	44	F	Mood-congruent psychotic	29	1,672	1,545	1,360	10,020
3	54	F		18	1,987	1,380	768	7,635
4	62	F		20	2,482	2,400	711	9,570
5	48	F	Melancholia	27	2,890	1,850	590	7,682
6	47	M		28	3,950	1,925	785	12,500
7	42	M		29	1,537	1,185	324	3,525
8	49	M	Melancholia	19	3,645	1,905	591	1,098
9	45	M		23	1,477	1,902	339	8,505
10	40	M	Melancholia	25	2,537	1,600	790	9,780
Mean				24.8	2,702	1,711	674	8,324
SD				4.4	1,135	357	297	3,675
Range					1,537-4,845	1,185-2,400	324-1,360	1,098-12,930
Control subjects								
Mean					5,984	2,717	730	9,186
SD					2,103	547	285	2,342
Range					2,362-8,530	1,470-3,525	285-1,135	7,125-13,830

sampling, an indwelling cannula was inserted into a forearm vein and connected with a long tubing extension placed through a soundproof lock in the wall into the neighboring laboratory where blood was collected. After blood was drawn for baseline ACTH and steroid determinations, an intravenous bolus of 100 μ g of human CRH was injected directly into the cannula at 7:00 p.m. Blood was collected every 15 minutes until 8:00 p.m. and every 30 minutes until 10:00 p.m. for multihormone analysis. During the entire experiment, an ECG was recorded and each blood collection was followed by an automatized blood pressure measurement. ACTH and steroid levels were determined with radioimmunoassay techniques, as previously described (5, 8). To exclude the possibility that differences in findings resulted from variable bioavailability of human CRH, the immunoreactivity of the neuropeptide was measured in the sample drawn 15 minutes after injection (8).

RESULTS

The net hormone responses to human CRH, calculated as areas under the time course curves, are presented individually and collectively for the 10 depressed patients and collectively for the control subjects in table 1. ACTH release was significantly blunted in depressed patients ($t=4.29$, $df=18$, $p<.01$), whereas both glucocorticoids failed to reveal markedly different release patterns after CRH injection. Aldosterone responses were significantly lower in the depressed patients than in the control subjects ($t=4.91$, $df=18$, $p<.01$). No adverse effects were noted, and blood pressures remained indistinguishable between

the two groups throughout the study. At baseline, plasma cortisol levels in the patients with depression were markedly higher than in the control subjects (71.9 ± 21.7 versus 50.1 ± 14.4 ng/ml; $t=2.7$, $df=18$, $p<.05$). Immunoreactive CRH content in the plasma samples drawn 15 minutes after CRH injection was 2.0 ± 1.6 ng/ml in depressed patients and 1.8 ± 0.6 ng/ml in control subjects, yielding no significant difference.

DISCUSSION

Our major finding, a significantly blunted aldosterone and ACTH response in depressed patients in contrast to normal cortisol and corticosterone release, adds to earlier reports of altered aldosterone regulation in affective disorders (4-6). Our data also amplify the impression that mineralocorticoid secretion is regulated by factors which are, at least in part, different from those which control glucocorticoid regulation (9). Whether diminished aldosterone output after human CRH injection directly results from decreased circulating ACTH concentrations or is an indirect result of disturbed hypothalamic-pituitary-adrenocortical feedback circuitry remains unresolved. However, the recent characterization of different mineralocorticoid receptor types (10) may provide a better understanding of these effects.

Our findings corroborate those from previous studies (1, 2) showing that elevated baseline cortisol decreases ACTH output by negative feedback action. Although less ACTH was secreted in patients with depression, release of both glucocorticoids was indistinguishable between the two groups. This supports

the hypothesis that sustained overactivity of pituitary corticotrophic cells and enhanced ACTH secretion are followed by a moderate functional hyperplasia of the adrenocortex (1, 2). As a result, depressed patients would require less ACTH to produce the same quantity of corticosteroids than would normal subjects.

The differential effects of glucocorticoid and mineralocorticoid responses in relation to ACTH release after human CRH administration have clinical implications for depression research and deserve further study in larger samples.

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Platelet Serotonin Concentration in Schizophrenic Patients

Tamara Kolakowska, M.D., and Stephen G. Molyneux, B.Sc.

Platelet serotonin (5-HT) concentration did not significantly differ between control subjects (N=45) and schizophrenic (N=62) or chronic schizophrenic (N=39) patients. No clinical feature was associated with hyperserotonemia, but the subgroup receiving benzodiazepines had a significantly higher 5-HT level than other patients.

(Am J Psychiatry 1987; 144:232-234)

There have been several reports that the concentration of serotonin (5-hydroxytryptamine, 5-HT) in whole blood or platelets is increased in chronic schizophrenic patients, both in those drug-free (1-3) and those receiving neuroleptics (4, 5). The reported clinical correlates of high 5-HT concentration, e.g., undifferentiated form of schizophrenia (4), abnormalities in computerized axial tomography (CAT) scans (5), and auditory hallucinations (3), suggest that hyperserotonemia may be either a biological marker of a subtype of schizophrenia or a state-related trait. However, none of these associations has been replicated. Moreover, in some studies (6, 7), the 5-HT concentration of chronic schizophrenic patients did not differ from that of control subjects. In view of these conflicting findings, we investigated platelet 5-HT concentration in schizophrenic patients and examined its associations with selected clinical features.

METHOD

Each of the 62 patients (37 men and 25 women; mean \pm SD age = 35 ± 10 years) met the Research Diagnostic Criteria (RDC) for schizophrenia (N=50) or schizoaffective disorder (N=12), had had the first psychotic episode more than 2 years previously

(mean \pm SD = 12.6 ± 8.7 years), was free of physical illness, and gave informed consent to participate in the study. The sample included hospitalized subjects (N=25), day patients (N=15), and outpatients (N=22). All but two were receiving neuroleptics, mostly fluphenazine decanoate (N=20), flupenthixol decanoate (N=27), and/or chlorpromazine (N=21); 27 were also receiving anticholinergic drugs for neuroleptic-induced parkinsonism, and 15 were taking benzodiazepine hypnotics. The control group consisted of 45 healthy volunteers (24 men and 21 women; mean \pm SD age = 31 ± 5 years).

Clinical assessment, carried out with the methods used in our earlier study (8), included ratings of psychiatric symptoms (Brief Psychiatric Rating Scale), parkinsonian symptoms, and abnormal movements. Twenty patients were in good remission, and the remainder were psychotic (N=21) or showed residual psychotic symptoms (N=21); 33 were resistant to neuroleptics; i.e., their symptoms had not changed during the most recent treatment with doses equivalent to at least 800 mg/day of chlorpromazine. Parkinsonian symptoms were present in 18 patients and tardive dyskinesia in nine.

The results of CAT brain scans were available for 22 patients who participated in our earlier study (8). In four, the ventricle-brain ratio (VBR) was more than two standard deviations from the mean of the control group ("high" VBR).

Venous blood samples were drawn between 9:00 and 10:00 a.m., mixed with EDTA, and centrifuged. Platelets were counted in a Coulter Thrombocounter. After separation of platelets by repeated centrifugation, platelet 5-HT was measured by high-performance liquid chromatography with electrochemical detection, as described elsewhere (9).

In 51 patients and 21 volunteers, samples were taken more than once. The intraindividual variations in platelet 5-HT concentration were 16.6% and 15%, respectively. As in other studies (1, 3), there was no difference in 5-HT concentration between fasting and nonfasting conditions (N=7; mean 5-HT = 3.57 and 3.56 nmol/ 10^9 platelets, respectively).

Two-tailed t tests were used to compare platelet 5-HT concentrations. Pearson's coefficients of correlation were computed to relate platelet 5-HT to other variables. The overall significance level was set at $\alpha = .05$. To protect against inflated type I error in the multiple t tests, the Bonferroni correction (10) was

Received Jan. 13, 1986; revised June 16 and Sept. 22, 1986; accepted Oct. 31, 1986. From the Department of Psychiatry, University of Oxford, Littlemore Hospital, Oxford, England. Reprints are not available; address correspondence to Dr. Kolakowska, Department of Psychiatry, Littlemore Hospital, Oxford OX4 4XN, England.

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TABLE 1. Platelet 5-HT Concentration in Schizophrenic Patients and Control Subjects^a

Group	All Subjects			Men			Women		
	N	Mean	SD	N	Mean	SD	N	Mean	SD
Control subjects	45	4.28	1.70	24	3.65	1.12	21	5.01 ^b	1.96
Schizophrenic patients	62	4.26	1.90	37	4.13	1.90	25	4.47	1.98
Benzodiazepine use									
Yes	15	5.80 ^c	2.49	9	5.75 ^d	2.49	6	5.86	2.81
No	47	3.77	1.42	28	3.52	1.49	19	4.03	1.49
Hallucinations									
Yes	24	4.72	2.10	14	4.16	1.50	10	5.51 ^e	2.55
No	37	3.97	1.80	23	4.09	2.13	14	3.63	0.98

^aTwo-tailed t tests were used to compare groups, and results with $p < .05$ are indicated. The Bonferroni correction is $0.05/10 = 0.005$ for the 10 tests in this table; it would be $0.05/18 = 0.0027$ if the additional eight comparisons listed in the text were considered.

^bHigher than for men ($t = 3.05$, $df = 43$, $p < .01$).

^cHigher than for control subjects ($t = 2.19$, $df = 58$, $p < .05$) and for other schizophrenic patients ($t = 3.25$, $df = 60$, $p < .002$; meets Bonferroni criterion).

^dHigher than for other male patients ($t = 2.56$, $df = 35$, $p < .02$).

^eHigher than for other female patients ($t = 2.24$, $df = 22$, $p < .05$) (one mute female patient omitted).

calculated to determine the significance levels required in individual tests.

RESULTS

Platelet 5-HT was unrelated to platelet count or age. The mean platelet 5-HT concentrations of the subject groups are presented in table 1. There was no difference between the patients and control subjects, regardless of whether the male and female subjects were compared separately or jointly. This remained true when the patient group was limited to those who met the RDC for chronic schizophrenia ($N = 39$; mean 5-HT = $4.09 \text{ nmol}/10^9$ platelets), those who were hospitalized ($N = 25$; mean 5-HT = $4.31 \text{ nmol}/10^9$ platelets), or those who were neuroleptic resistant ($N = 33$; mean 5-HT = $4.37 \text{ nmol}/10^9$ platelets). Although the patients receiving benzodiazepines had a higher 5-HT concentration than the control subjects, the difference did not reach the Bonferroni criterion of significance ($t = 2.19$, $df = 58$, $p < .05$) (see table 1). The 5-HT concentration of the benzodiazepine group was, however, significantly higher than that of the remaining patients ($t = 3.25$, $df = 60$, $p < .002$) according to the Bonferroni criterion. These two groups of patients did not differ in other medication, age, or clinical features. We found no relationship between 5-HT concentration and either neuroleptic medication (drug, dose) or anticholinergic drugs.

Platelet 5-HT did not differ between patients categorized by remission versus psychosis, schizophrenia versus schizoaffective disorder, parkinsonism, and tardive dyskinesia, but the presence of hallucinations among female patients appeared to be associated with a higher 5-HT concentration ($t = 2.24$, $df = 22$, $p < .05$; nonsignificant according to Bonferroni correction). Among 22 patients whose CAT scans were examined, there was no correlation between 5-HT concentration

and VBR ($r = .15$) and no difference in 5-HT between the subjects with high VBRs ($N = 4$) and the remainder ($N = 18$) (mean \pm SD 5-HT = 3.50 ± 1.80 and $4.61 \pm 2.00 \text{ nmol}/10^9$ platelets, respectively).

DISCUSSION

The main findings of our study are as follows: 1) 5-HT concentration did not differ between schizophrenic and control subjects, 2) it was not abnormally high in the patients who met the RDC for chronic schizophrenia, and 3) none of the examined clinical features, including resistance to neuroleptics, was associated with higher platelet 5-HT concentration. It is unlikely that the discrepancy between these results and the reports of hyperserotonemia in chronic schizophrenic patients could be due to the fact that our patients were receiving neuroleptic drugs when studied. First, hyperserotonemia has been reported in neuroleptic-treated groups (4, 5), and normal 5-HT concentrations have been found in drug-free samples (6). Second, there is consistent evidence (2–5, 7) that neuroleptic treatment does not alter serotonin concentration, and accordingly, we have found no association between platelet 5-HT and neuroleptic dose. It seems more likely that some characteristics of the patients may be important for the discrepant 5-HT findings. In one study (3) the reported higher 5-HT level was significant only for the subgroup of black schizophrenic patients, and in another (5) it was limited to patients with abnormal CAT scans, who constituted 66% of the sample. All our subjects were Caucasian, and the proportion of those with enlarged brain ventricles was small. Our failure to replicate the reported relationship between VBR and platelet 5-HT concentration could be due to the small number of patients with enlarged ventricles, which was also found in another study with a negative result (3). The tendency

toward a higher platelet 5-HT concentration in patients with auditory hallucinations, although found only among our female patients and not meeting the Bonferroni criterion for significance, is of interest as it corresponds to the findings of Jackman et al. (3).

The unexpected finding of a significantly higher 5-HT concentration in the group receiving benzodiazepines than in the remaining patients has to be regarded with caution. To our knowledge, there are no published data on the effect of benzodiazepines on platelet 5-HT level. An independent study designed as a within-subject comparison is needed to indicate whether these drugs increase platelet 5-HT.

The results of this study do not support the hypothesis that chronic schizophrenia or its particular clinical features are associated with a high platelet 5-HT concentration. The conclusions from these negative findings should not, however, be generalized and would be of limited validity for a population of patients with characteristics that are not represented in our sample.

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Clonidine in Neuroleptic-Induced Akathisia

Lenard A. Adler, M.D., Burt Angrist, M.D., Eric Peselow, M.D.,
John Reitano, M.D., and John Rotrosen, M.D.

Six hospitalized patients with neuroleptic-induced akathisia were treated with clonidine under single-blind conditions. Akathisia and anxiety at maximum clonidine dose were significantly lower than at baseline, although it was difficult to differentiate specific therapeutic effects from sedation.

(Am J Psychiatry 1987; 144:235-236)

Recent studies have shown that the β -adrenergic blocker propranolol is a safe and effective treatment for neuroleptic-induced akathisia. Lipinski, Zubenko, and their colleagues (1-3) originally reported open studies in which low doses (30-80 mg/day) of propranolol dramatically ameliorated akathisia. We have also documented the efficacy of propranolol in treating akathisia under single-blind (4) and double-blind, placebo-controlled (5) conditions. These studies suggest that an interaction between the noradrenergic and dopaminergic systems might be a factor in the pathophysiology of akathisia. The importance of dopaminergic-noradrenergic interactions in akathisia is further suggested by an open study by Zubenko et al. (6) showing that the α_2 -agonist clonidine, which decreases central noradrenergic transmission (7), effectively treated akathisia.

To further examine the role of noradrenergic mechanisms in akathisia, we conducted a pilot study of clonidine in the treatment of this syndrome.

METHOD

Inpatients receiving neuroleptics were enrolled if they showed akathisia-like movements that were given

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ratings of at least 1 ("mild, occasional restlessness observed during exam and/or subjective report of definite restlessness") on a modification of the original Simpson/Angus extrapyramidal symptom scale (8). Six subjects participated; all were male and they ranged in age from 23 to 59 years. Their DSM-III diagnoses were chronic schizophrenia (N=4), bipolar disorder, manic type (N=1), and schizoaffective disorder (N=1). All patients were receiving oral neuroleptics, which included fluphenazine, perphenazine, mesoridazine, and chlorpromazine. The mean dose of neuroleptics in chlorpromazine equivalents was 647 mg/day. The patient with bipolar disorder was also being treated with lithium carbonate, 1200 mg/day. Three of the six patients were also receiving antiparkinsonian agents (diphenhydramine and/or benztropine). All medications were held constant throughout the trial.

Before entering the study, each patient received a physical examination, ECG, and evaluation by a cardiologist. Two patients had concomitant medical illnesses. One had essential hypertension, which was treated with hydrochlorothiazide, 100 mg/day; the second patient had diabetes mellitus, which was controlled with NPH insulin, 20 U/day, and regular insulin, 6 U/day.

Clonidine was prescribed by an investigator who did not rate the patients. The initial dose was 0.05-0.20 mg/day; the dose of clonidine was adjusted on the basis of both effects on akathisia and side effects (sedation and hypotension) over 3-15 days (mean \pm SD = 6.7 \pm 4.3 days) to a maximum tolerated dose of 0.15-0.40 mg/day. Clonidine was then slowly tapered to zero over several days.

The ratings consisted of the following: 1) an objective rating on the modified Simpson/Angus extrapyramidal symptom scale, 2) a subjective score by the subject, who was asked to mark a 100-mm line corresponding to perceived restlessness, and 3) the score on the Hamilton anxiety scale (9).

Ratings were performed at baseline and 2-3 times per week by one of two physicians who did not know when clonidine treatment was to begin. Clonidine treatment was started 1-3 days after the ratings began, and the ratings continued for 3-13 days (mean \pm SD = 7.3 \pm 4.6 days) after clonidine was discontinued.

The study was approved by the Subcommittee for Human Subjects at the New York VA Medical Center. Each subject signed a consent form after discussion of the potential risks and benefits with his physician.

TABLE 1. Effect of Clonidine on Neuroleptic-Induced Akathisia and Anxiety in Six Patients

Patient	Baseline			Early Clonidine Treatment (day 2-4) ^a				Maximum Clonidine Dose ^b			
	Akathisia Rating		Anxiety Rating	Dose (mg/day)	Akathisia Rating		Anxiety Rating	Dose (mg/day)	Akathisia Rating		Anxiety Rating
	Subjective	Objective			Subjective	Objective			Subjective	Objective	
1	80	2	7	0.20	20	2	4	0.20	20	1	1
2	60	2	13	0.20	50	2	9	0.20	40	1	5
3	60	2	12	0.10	60	2	14	0.40	40	0	12
4	95	2	11.5	0.15	10	0	4	0.20	10	1	4
5	80	3	17	0.15	58	2	12	0.20	48	1	17
6	60	3	15	—	—	—	—	0.15	2	0	8
Mean	72.5	2.3	12.6	0.16	49.6	1.6	8.6	0.23	26.7	0.7	7.8
SD	14.8	0.5	3.4	0.04	23.3	0.9	4.6	0.09	18.7	0.5	5.9

^aEarly clonidine treatment versus baseline (paired Student's *t* test, two-tailed)—subjective akathisia: *t*=1.66, *df*=4, *n.s.*; objective akathisia: *t*=1.50, *df*=4, *n.s.*; anxiety: *t*=2.24, *df*=4, *n.s.*

^bMaximum clonidine dose versus baseline (paired Student's *t* test, two-tailed)—subjective akathisia: *t*=4.30, *df*=5, *p*≤.008; objective akathisia: *t*=5.00, *df*=5, *p*≤.005; anxiety: *t*=3.11, *df*=5, *p*≤.026.

RESULTS

Table 1 shows the dose of clonidine and ratings of subjective akathisia, objective akathisia, and anxiety for each patient 1) at baseline, 2) early in clonidine treatment (range=2-4 days, mean±SD=2.6±0.9 days), and 3) at maximum dose of clonidine. A rating early in the course of clonidine treatment was not obtained for one patient. The measures of subjective and objective akathisia and anxiety at the maximum tolerated doses of clonidine were significantly improved from baseline; there was a nonsignificant decrease in akathisia and anxiety ratings early in clonidine treatment.

The baseline scores did not significantly differ from later ratings done when the patients were not being treated with clonidine. It should also be noted that the dose of clonidine was limited by hypotension in five patients and by clinically obvious sedation in four subjects.

DISCUSSION

Although conclusions based on such a small and heterogeneous sample must be viewed tentatively, clonidine (at maximum tolerated doses) did significantly ameliorate both subjective and objective measures of akathisia. An effect was seen early in the course of treatment, and it appeared to increase when the dose was raised. Also, clonidine had a small but significant effect on anxiety ratings; this differs from our findings with propranolol (5), which markedly reduced akathisia but did not significantly lower Hamilton anxiety scores.

These data and other observations of improvement in akathisia after treatment with clonidine (6) or β -blockers (1-5) support a role for noradrenergic mechanisms in the etiology of akathisia.

The sedation we observed after clonidine treatment raises two important caveats: 1) this sedation was clinically apparent to the raters and compromised the

blind quality of the ratings in some patients and 2) sedation might in itself be expected to ameliorate both akathisia and anxiety to some degree. In fact, in most subjects the decrements in subjective measures of akathisia and Hamilton anxiety scores were strikingly parallel. Therefore, it is difficult to determine whether these data reflect specific pharmacologic antagonism or merely nonspecific sedative effects.

These problems might be resolved in the future by studying the effects of 1) transdermally applied clonidine (which should produce more steady plasma levels and therefore less sedation than oral clonidine) or 2) less sedative α_2 -agonists, such as lofexidine.

Finally, it should be noted that as a practical treatment of akathisia, clonidine was more difficult to use than propranolol, which in the doses studied to date has not caused sedation and hypotension (1-5).

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Allergy to Tartrazine in Antidepressants

Robert Pohl, M.D., Richard Balon, M.D.,
Richard Berchou, Pharm.D., and Vikram K. Yeragani, M.D.

The authors describe five cases of apparent allergy to tartrazine (FD&C yellow dye number 5) in 170 patients exposed to the dye in antidepressants. The frequency of tartrazine sensitivity was much higher than the reported frequency of six in 1,000 persons. (Am J Psychiatry 1987; 144:237-238)

Allergic reactions to antidepressants are frequently the result of an allergy to a dye rather than to the active drug. Tartrazine (FD&C yellow dye number 5) is the most frequently implicated (1, 2). Urticaria, bronchospasm, and nonthrombocytopenic purpura are the most frequently described symptoms, but angioedema, rhinitis, and anaphylaxis can occur (3, 4).

Adverse reactions to tartrazine occur more frequently in people with aspirin sensitivity, but a chronic urticaria without aspirin intolerance can occur (5). Tartrazine and other dye sensitivity has been estimated to occur in only one out of 10,000 persons (6) but has been reported in as many as six in 1,000 (7). We describe five cases of urticaria associated with administration of tricyclic antidepressants. These cases were culled from a review of 262 patients prescribed tricyclic antidepressants.

METHOD

The medical records of 262 patients who were prescribed tricyclic antidepressants were reviewed after the exclusion of patients with a history of psychosis, organic brain syndromes, or drug abuse. Patients who took only brand-name tricyclics known to not contain tartrazine and patients who were lost to follow-up after the first visit were excluded. From the original group, 170 patients were exposed to tricyclic antidepressants that might have contained tartrazine. These included imipramine and desipramine, name brands of which both contain the dye, and amitripty-

line, which, like imipramine and desipramine, is available in generic forms that may contain the dye.

Of the 170 patients, 137 were exposed to imipramine, 64 to desipramine, and 11 to amitriptyline. These numbers total more than 170 because 42 patients were exposed to more than one of these drugs. The patients were taken from a single private practice of one of us, who specializes in the treatment of panic disorder. There were 136 patients with panic disorder, 24 patients with major depressive disorder, and 10 patients with other diagnoses. There were 104 women and 66 men, age 12 to 78 years (mean \pm SD=36.7 \pm 12.6).

RESULTS

Five of the 170 patients exposed to tricyclic antidepressants that might contain tartrazine developed urticaria that appeared to be an allergic response to dye. A commonly reported frequency of tartrazine allergy is 1:10,000 (6), but in a study using repeated tartrazine challenges (7), the frequency was reported to be 6:1,000. The 5:170 frequency in our study was significantly greater than the highest reported frequency of 6:1,000 ($\chi^2=8.55$, $df=1$, $p<.01$).

CASE REPORTS

Case 1. Ms. A, a 31-year-old woman with panic attacks, was treated with generic imipramine. During the first few days she developed a rash on her arms, but it disappeared after a few days. After 12 days she was up to four 25-mg yellow tablets but complained of itching all over her body. She said the itching was so severe that she would "rather have poison ivy." The pruritis was accompanied by a rash on her arms, legs, epigastric area, and chest. She denied any similar symptoms with aspirin, although she did complain of nausea due to aspirin and avoided it. She was switched to a brand of desipramine that lacked tartrazine and did not have any recurrence of her symptoms.

Case 2. Ms. B, a 20-year-old woman with panic attacks, was started on generic imipramine. She took 10 mg one day and 20 mg the next day. She then developed a rash on her thighs, popliteal surface, and the anterior surface of her forearms. She had itching over her trunk but no rash. The symptoms disappeared when imipramine was discontinued; 2 weeks later she was prescribed a brand of desipramine

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without tartrazine and had no recurrence of her symptoms. She had no history of sensitivity to aspirin.

Case 3. Ms. C, a 26-year-old woman with panic attacks, also had a 4-month history of hives; however, she had been free of this symptom for 1 month. She was placed on a regimen of generic imipramine and took a 10-mg yellow tablet the first day and increased the dose by 10 mg daily. She called after 1 week to report that she had developed a rash over her entire body and at the same time revealed that she was allergic to aspirin. She was switched to 10-mg tablets of desipramine but was lost to follow-up.

Case 4. Ms. D, a 19-year-old woman with a bipolar affective disorder, was asymptomatic while taking doxepin and lithium carbonate; both drugs lacked tartrazine. Because of weight gain, she was gradually switched to 300 mg/day of a brand of desipramine with tartrazine. She developed a generalized body rash and pruritis within 2 weeks. She then revealed a history of allergy to aspirin and was prescribed a brand of desipramine lacking tartrazine, and she did not experience any recurrence of her rash.

Case 5. Ms. E, a 22-year-old woman with panic attacks, received desipramine that contained tartrazine and developed a generalized body rash within a few days. The rash subsided after the drug was discontinued, and she had no subsequent dermatological symptoms with antidepressants that lacked the dye (brand-name amitriptyline and maprotiline).

DISCUSSION

In all five patients tricyclic antidepressants were associated with a skin rash. Allergy to tartrazine appeared to be the most likely explanation in each case. At least two of the three patients given generic imipramine were taking yellow tablets, and one of these had a history of allergy to aspirin. Two patients developed a rash after taking brand-name desipramine known to contain tartrazine; one had a history of aspirin allergy. Four of the five patients were followed up long enough to confirm that tricyclic antidepressants which did not contain tartrazine were not asso-

ciated with any symptoms of drug sensitivity. Unfortunately, no brand-name imipramine without yellow dye was available to rechallenge the patients who were taking generic imipramine.

The frequency of tartrazine-induced urticaria in this sample was greater than could be expected by chance alone if tartrazine sensitivity occurred in only six out of 1,000 individuals and much greater than the usually reported incidence of 1:10,000. If it is assumed that panic disorder by itself is not a risk factor, then the frequency of allergic responses to tartrazine in the population may be far greater than previously reported.

If tartrazine sensitivity has a frequency closer to 1:34 than 1:10,000, there are a number of clinical implications. First, the patients with allergic responses to antidepressants that contain tartrazine are likely to tolerate similar or identical drugs that lack tartrazine. Second, clinicians should routinely ask at least patients with multiple allergies about allergy to aspirin. If a clinician wants to prescribe a tartrazine-free antidepressant, generic drugs should be avoided. Drug companies often list tartrazine as an additive in their package inserts, and this information is readily available for brand-name drugs. Tartrazine will soon be removed from at least two brand-name drugs, Tofranil and Norpramin.

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Book Forum

Nancy C. Andreasen, M.D., Ph.D., Editor

ALCOHOLISM

Alcohol: Use and Abuse in America, by Jack H. Mendelson and Nancy K. Mello. Boston, Little, Brown & Co., 1985, 416 pp., \$25.00.

The objectives of this monograph are to put contemporary American drinking practices and problems within a historical context and to integrate recent alcohol-related research in medicine, biology, psychology, and the social sciences. American Colonial society did not oppose drinking, but drunkenness was severely punished. Alcohol remained a central feature of American life after independence. At the end of the eighteenth century the estimated alcohol consumption reached nearly six gallons of absolute alcohol per adult, more than twice the current American usage. In the early nineteenth century, the United States became known as a nation of drunkards.

Benjamin Rush was one of the first to consider intemperance a disease; he became the father of the American temperance movement. Although he died in 1813, Rush's scientific authority was cited in the advice to abandon the widespread practice of providing free liquor to laborers. By the 1830s, drunkenness was the largest category of criminal offense in Boston, New York, and Philadelphia, and at Pennsylvania Hospital and McLean Hospital, alcohol-related mental illness accounted for more admissions than any other type of mental disorder. By that time, temperance organizations, with strong participation by the nation's Protestant churches, were claiming that any kind of involvement in the liquor business was incompatible with Christian morality. As the temperance movement broadened its base, liquor consumption dropped 75% by mid-century. Local option laws were passed in towns and cities prohibiting the sale of alcoholic beverages. Those who advocated total abstinence became known as "teetotalers." By 1855, 13 states forbade the manufacture and sale of intoxicating liquors. By 1863, however, only five did so. The temperance movement splintered as social interest turned to the slavery question and the war.

It was not until the 1870s that temperance reform regained its vigor. Women's crusades against alcohol led to the formation of the Women's Christian Temperance Union, the first mass movement of women in American history. Mendelson and Mello describe all of this and the growing social march toward the Eighteenth Amendment in 1919 and Prohibition in an easy yet detailed style. The entire first third of their book is devoted to the historical review. They go on to describe contemporary drinking patterns and the fact that a concern for health rather than sin is the conceptual basis of those who combat alcoholism today.

The last chapter of part one deals with regulation of the alcoholic beverage industry from the local to the federal level. Extensive statistics on production, tax revenues, and consumption are included, as well as an in-depth state-by-state summary of drinking laws.

Part two, entitled *Alcohol: Biology and Behavior*, assumes

no medical expertise on the part of the reader but is nonetheless instructive to the physician who does not specialize in the treatment of alcoholism. The discussion of alcohol metabolism follows the molecule from its passage through the pylorus to the complicated processes involved in its inactivation and excretion. The depth of the new evidence about alcohol's effect on luteinizing hormone, testosterone, and male feminization is disappointing, largely because of the paucity of research. Research on alcohol's effects has tended to ignore women almost totally until recently. Especially unstudied is alcohol's effect on sexual arousal in both men and women.

Mendelson and Mello challenge the common belief that alcohol intoxication regularly produces even a transient state of happiness. Research conducted while subjects were intoxicated has repeatedly demonstrated that alcohol often produces dysphoria, depression, and anxiety. Subjects, however, remember the anticipated pleasure, not the actual displeasure. To explain continued drinking despite the pain, the authors suggest the concept of "stimulus self-administration" with the goal of state change. "At least it's different," and "different," they claim, may be the reinforcer of the drinking.

Part three deals with the role of alcohol in sickness and health. Cancer and disorders of the heart, the gastrointestinal system, the brain, and the reproductive system are discussed. Seen as a hypnotic for millennia, alcohol changes sleep patterns so that they resemble those of an elderly person. Even a single drink in the evening can decrease REM sleep to a subnormal level. Many depressed people find that abandoning the alcohol they use to self-medicate paradoxically causes improvement in depression and/or insomnia.

Chapter 14, which deals with the search for origins of alcoholism, is based on a previously published monograph by Mello. Little is really known other than the fact that alcoholism in a biological parent is a better predictor of alcoholism than any social or environmental factors. More prospective studies are needed. Until recently, physicians argued against alcohol as the agent responsible for withdrawal syndromes, favoring poor nutrition and other extraneous factors. The demonstration that alcoholism is an addiction manifested by withdrawal and tolerance was decisive in supporting the disease concept of alcoholism. The book's section on treatment and prevention are thin, however, again because of the paucity of scientific fact. Mendelson and Mello see multimodality treatment as preferable to any single therapy.

Recent assessment of the prevalence of mental disorders in the United States found alcohol abuse and dependence to be the most common form of mental disorder among men. This book by Mendelson and Mello is much needed. I hope that it will be recommended by psychiatrists to other mental health professionals and appropriate laypersons. They are the readership for whom it is primarily intended.

JEROME D. WINER, M.D.
Chicago, Ill.

The American Experience With Alcohol: Contrasting Cultural Perspectives, edited by Linda A. Bennett and Genevieve M. Ames. New York, Plenum, 1985, 490 pp., \$49.50.

The title of this important volume contains two perplexing notions: What does the adjective "American" mean? And, among the world's artifacts, what is more difficult to understand than alcohol, a substance that has at times been called everything from the blood of a god to a horrible demon?

Although the Americans in this book are presented in terms of gender, age, and social class, major consideration is given to religion and ethnicity. The religious groups examined are Irish-American Catholics, Episcopalians, and middle-class Protestants. Also examined are Italian, Polish, Jewish, Appalachian, black, Mexican, Japanese, Navajo, Hispanic, Cuban, and Hmong (Laotian) ethnic groups. In 24 chapters by different authors, the book presents each group's alcohol-related beliefs and experiences with problem drinking and chronic alcoholism and demonstrates the significance of cultural patterning for treatment of alcohol problems.

The rich cultural pluralism of the United States defies any simplistic conclusions about a unique or mainstream national mode of drinking. Even among members of an ethnic group, drinking styles are often related to generation. First-generation Italians, for example, drink moderate amounts of wine and rarely get intoxicated, while third-generation Italians tend to consume beer and hard liquor and are experiencing problem drinking and alcoholism. Drinking among the Hmong, as ably described by Joseph Westermeyer, has developed several patterns. In traditional Hmong culture, alcohol was a desired, valued, and powerful substance whose use was governed by group and societal customs. Problems with alcohol began to emerge because of technological and social changes; e.g., dangerous accidents occurred when intoxicated drivers switched from slow, safe, and intelligent ponies to swift, dangerous, and unthinking motorized vehicles. Hmong in the United States have substituted alcohol for opium and use it for medicinal and recreational purposes. Fearful of alcohol's destructive potential, some Hmong are now calling for total abstinence rather than insisting on a return to socially controlled ritual drinking.

In addition to examining current cultural patterns, the book's contributors often supply historical contexts. In Colonial America, for example, alcohol consumption was heavy but not particularly problematic. Puritan ministers often described alcohol as the "good creature of God" that was no more responsible for drunkenness than food was for gluttony. Drunkenness was regarded as a personal indiscretion. As alcohol consumption escalated, drunkenness became a genuine social problem. Religious groups denounced demon rum and equated abstinence with virtue and salvation. Benjamin Rush conceptualized drunkenness as a "disease of the will." Temperance became a sign of respectability that distinguished the established middle-class from the lower-class Irish and German immigrants. When Prohibition came, physicians lost their interest in alcoholism, and alcohol treatment facilities closed their doors. Medical interest returned when Jellinek forcefully described alcoholism as a progressive disease, but the divergent views of the moral and medical models still influence both the general public and health care professionals. How responsible is the alcoholic for his or her condition? How much of the condition is due to moral weakness? How much to biological forces? Alcoholics Anonymous (AA) regards alcoholism as a lifelong disease, yet its tone is religious. In one of the book's most

important chapters, Miriam Rodin provides a biocultural analysis of AA meetings and demonstrates the relationship between cognitive impairment in newcomers and the ritual formulas and clichés of the group leaders.

This is an exceptionally rich book. Its major flaw, as noted by Dwight Heath in the concluding chapter, is that "we have little indication of the extent to which the respondents the studies reported reflect the overall population, and none of the contributors' reports having attempted any systematization in terms of sampling behaviors." Now that new ground has been broken, however, we can expect this problem to be remedied in future studies.

ARMANDO R. FAVAZZA, M.D.
Columbia, Mo.

Practical Approaches to Alcoholism Psychotherapy, 2nd ed., edited by Sheldon Zimberg, M.D., John Wallace, Ph.D., and Sheila B. Blume, M.D. New York, Plenum, 1985, 406 pp., \$24.50.

While perusing this text prior to a thorough reading, I was struck by John Wallace's comment, "In alcoholism psychotherapy, neither irrational guilt nor sociopathic values are to be encouraged" (p. 39). He does not, however, conjecture about the clinical conditions or circumstances in which irrational guilt or sociopathy is recommended. Apparently, what is encouraged in the treatment of alcoholism, according to the editors of this book, is a potpourri of contemporary therapies—for example, psychodynamic psychotherapy, behavioral therapy, and group therapy and its variations (e.g., family therapy and psychodrama). Based on the disparate modes of therapy considered, it is obvious that the editors maintain that more treatment is better treatment; hence, applying a smattering of therapies, perhaps calling that amalgam a "treatment program," the prospects for helping the individual remain abstinent from alcohol are measurably improved. Presented here is the "every little bit helps" approach to treatment without particular concern for such issues as patient-treatment matching, defining and measuring the behaviors targeted for change, monitoring the progress of change, and operationally defining the criteria for a successful outcome. The focus is simply on "doing it," without regard to an explicit rationale for what should be done or for evaluating the consequences of the effort. The paucity of data and only superficial reference to the abundant research literature on the recovery process in alcoholism suggest that accepted empirical standards for appraising treatment efficacy are of little concern to the editors.

Thus, as a work of scholarship this book is a disappointment; it fails in its objective because the recommended practical approaches to alcoholism treatment are neither built on a foundation of empirical research nor integrated systematically into a theoretical conceptualization of alcoholism etiology. The senior editor's thesis that alcoholism emerges as the consequence of unresolved dependency needs and conflicts requiring a psychotherapeutic strategy that can break through "reactive grandiosity" (p. 9) for successful treatment is, to say the least, highly arguable in the light of the research evidence accrued during the past two decades.

This text may be suitable for the paraprofessional or for the reader who mostly seeks a description of several of the more popular forms of didactic therapy. Although not comprehensive, the chapters are clearly written, and several of them address the specific problems of underserved popu-

lations such as female, elderly, and sexually disabled alcoholics, as well as children of alcoholics.

RALPH E. TARTER, PH.D.
Pittsburgh, Pa.

PERSONALITY DISORDERS

Treatment of the Borderline Personality, by Patricia M. Chatham. New York, Jason Aronson, 1985, 585 pp., \$40.00.

For those of us who entered psychiatry 25 years ago, the then newly developing concept of borderline personality disorder was enormously helpful in our efforts to come to terms with patients whose untoward, unexpected response to psychotherapy was close to incomprehensible. Earlier material from psychoanalysis that elucidated such phenomena as negative therapeutic reactions as interpretable in relationship to unconscious guilt did little to help us comprehend this group of patients. For them, intensive involvement with the therapist seemed ultimately to cause more problems within the transference than could be solved through its interpretation. The concept of a kind of stable instability that reflected a more limited ego which regressed rapidly and uncontrollably under the influence of psychotherapeutic closeness was helpful in sustaining the therapeutic intent for many therapists attempting to persist in their treatment efforts with such patients.

Since that time, the borderline personality disorder literature has rapidly increased. The last year alone has seen the publication of major texts by Kernberg, Meissner, Adler, and Willick, all concentrating on the treatment of the borderline patient. Emphasis on treatment has been at the leading edge of interest in this disorder because it is in treatment efforts that most clinicians have encountered the difficulties which, in turn, have engendered a special interest in understanding the enigma of this disorder.

In this extensive new volume by Patricia Chatham, we have an almost complete sampling of what a new generation of clinicians can assimilate to help them with the task of treating patients with borderline personality. Dr. Chatham has undertaken the task of reviewing most of the important psychodynamic contributions to the literature on the subject of the borderline personality. What she culls from the literature and applies in her clinical work includes important but often contradictory approaches, which she attempts to synthesize despite seemingly irreconcilable differences. Although her main interest is in elucidating a variety of psychodynamic contributions, she includes descriptive and psychobiological contributions as well. Since none of the material included in the chapters on diagnosis, psychoanalytic developmental theory, or object relations theory is original or difficult to find in its primary source, it is unclear what the purpose of the author's efforts is. The book at times seems more an effort to explore through the literature what the borderline personality concept is about than an original contribution. This impression is further supported by the author's deferential attitude to the authorities she so extensively quotes as the "masters" to whom she is indebted for their theories and to whom she looks for validation of her own clinical efforts. In her review of the psychoanalytic developmental literature, Dr. Chatham selectively focuses on the separation-individuation theory of Margaret Mahler. Unfortunately, she treats separation-individuation, with its

various subphases, as if the psychopathology of the borderline patient can be clearly connected to the difficulties at a particular subphase, a connection that Mahler herself came to question. The relevance of Kernberg's object relations theory to borderline patients is well summarized, which is not surprising because Dr. Chatham repeatedly stresses her preference for Kernberg's views.

Dr. Chatham allocates a large amount of space to the consideration of what she sees as competing schools of treatment of borderline patients. Here she follows the lead of Rinsley and Masterson, who themselves have presented their view of psychotherapy of the borderline patient as a special method or school of psychotherapy. Although many individuals have presented contributions from their experience relative to how to treat patients in the borderline category, the elevation of any one person's contributions into a school of thought seems to me to be premature and more related to personal wish than to actual fact. Dr. Chatham states that she is most influenced by and prefers the contributions of Kernberg, Rinsley, and Masterson. By this she means that some aspect of their interpretive, confronting approach to borderline patients seems to her to fit best the clinical dilemmas encountered with borderline patients. In her clinical examples, her attempts to explain and interpret the behavior of seemingly untreatable patients through the interpretation of primitive instincts seem to me more a valiant effort to rationalize a therapist's persistence in treatment efforts beyond the patient's actual potential for this style of treatment than it does a correctly used or understood interpretation.

The author briefly summarizes Kohut's theoretical contributions, but she fails to take into account Kohut's final thinking about borderline patients set forth in *How Does Analysis Cure?* (1), published posthumously. There he stated that, in essence, the absence of reasonably correct therapist empathy is what determines whether an otherwise treatable narcissistic patient will be converted into an untreatable borderline individual. Any other mode of interacting with narcissistically vulnerable patients, in Kohut's opinion, causes the emergence of a borderline personality disorder, which he came to see as an iatrogenic disorder.

It is not clear to me whether the author's efforts to master the psychoanalytic literature on borderline patients have been a help or a hindrance to her in evolving her own style of work. In her approach to the individual psychotherapy of the borderline patient, she uses what she refers to as "the mixed model approach." In this model, she attempts to use contributions from Kernberg, Masterson, and Meissner as well as from Kohut, Modell, and Winnicott. But the inherent contradictions in these approaches, particularly in their incompatible views of etiology and technique, cannot be overcome. Dr. Chatham is eager to use what she has learned from her study of various experts, but in so doing she illustrates some of the pitfalls that studying the experts may engender. Simultaneously to emulate those clinicians who conceptualize in terms of the holding environment (Modell) or self-object (Kohut), those who see the need for a "corrective emotional experience" as central to therapeutic needs, and those who see the need to confront, contain, and integrate the patient's aggression through vigorous interpretation of splitting and other so-called primitive defenses is simply impossible. The author's mixed model approach seems to me to be an unworkable conglomerate that is likely to result in an unintegrated therapeutic sensibility, even for those capable of achieving such a state through the use of clinical intuition.

Despite these significant problems, *Treatment of the Bor-*

derline Personality is likely to be a popular book. Its appeal stems from the author's willingness to read and summarize, almost in its entirety, the borderline personality literature. This task is far beyond the time limitations imposed on most clinicians. Thus, Dr. Chatham has performed a service for us all—providing in one volume much of the psychodynamic thinking available on the borderline patient. The completeness of her summary, however, inadvertently illustrates the degree to which the concept of borderline personality has been the victim of theoretical "overkill," which is increasingly dangerous for the maintenance of an open, explorative approach to the analytic psychotherapy of this patient group.

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HENRY J. FRIEDMAN, M.D.
Cambridge, Mass.

Obsessive-Compulsive Disorder: Psychological and Pharmacological Treatment, edited by Matig Mavissakalian, Samuel M. Turner, and Larry Michelson. New York, Plenum, 1985, 257 pp., \$29.50.

This book on the treatment of obsessive-compulsive disorder heralds the development of effective therapies for an illness long regarded as tortuous, crippling, and resistant to change. If we are to accept this remarkable achievement we will have to overcome a pessimism about the disorder that is deeply ingrained. But believe it we must. Actually, we are told that spontaneous remissions occur in a proportion of obsessional patients, but figures are variable and we remain uncertain about the natural history of the disorder. Regardless, there is evidence that roughly two-thirds of patients with obsessions and compulsions improve with exposure plus response prevention, the most effective form of behavior therapy. And, importantly, follow-up studies show that the benefits from this therapy are sustained. Beyond this, the distinguished contributors to this volume disagree. Rachman and Foa et al., for example, claim that patients with obsessive-compulsive disorder are unlikely to be helped by interpretive psychotherapy, yet Sifneos refers to it as a treatment of choice. Also, although Salzman states that drugs have no value beyond their effects on anxiety or depression, Ananth claims that clomipramine has antiobsessional properties. According to Rachman, there is little justification for the use of psychosurgery, but Ananth describes stereotaxic tractotomy as a valuable procedure of last resort.

To some extent these views reflect the bias of particular authors, but they call attention to the limitations of available data. Clearly, effective treatment exists, but which treatments or combinations are best and how to select those who will respond remain unclear. Most of the authors in this book deal with this uncertainty in a thoughtful and scholarly manner. They critically review the data, noting methodologic problems that limit the generalizability of findings. In addition, introductory and concluding chapters framing the discussions of psychotherapy, behavior therapy, pharmacological therapy, and psychosurgery point to the limits of our understanding of obsessive-compulsive disorder and highlight current issues and directions for future research. It is refreshing to see the proponents of various forms of therapy

cooperating to present such a balanced view. They promote an open-mindedness that will, in turn, benefit patients with this condition.

Although we welcome therapeutic developments for what was long considered a treatment-resistant condition, our enthusiasm must be tempered. A substantial proportion of patients improve, but most remain symptomatic and impaired to some degree. In addition, the various forms of treatment have their drawbacks. Behavior therapy is of little benefit for patients without avoidant behavior or rituals. Also, patients with secondary depression respond poorly to this treatment, and, of course, those who refuse it are not helped. Pharmacological therapy, when effective, is likely to be long-term because relapse usually follows the discontinuation of drugs. When drugs are administered chronically, side effects may become a problem. Clomipramine, for example, can cause lethargy, weight gain, sexual dysfunction, and constipation. Given these limitations, treatment should be multidimensional and the emotional and intellectual resources of the patient and his or her family should be mobilized for a concerted effort. Patients should be made aware of treatment limitations and encouraged to keep an open mind to therapies that have been shown to work.

Because we can help a great many obsessive-compulsive patients, we can expect new interest in the disorder to develop and, with it, still further advances in our understanding of the illness and its treatment. This book will do much to stimulate the interest, if not the enthusiasm, of researchers and clinicians.

RUSSELL NOYES, M.D.
Iowa City, Iowa

Personality and Its Disorders: A Biosocial Learning Approach, by Theodore Millon and George S. Everly, Jr. New York, Halsted Press (John Wiley & Sons), 1984, 272 pp., \$17.95 (paper).

This book was designed to be an introduction to personality disorders. It starts with a brief discussion of the nature of personality and a short discussion of the classification problems involved with personality disorders. The bulk of the book is then spent in the discussion of the individual personality disorders. It is well organized and easy to read.

The disorders discussed are defined by Millon's theoretical system. There are many similarities with *DSM-III* personality disorder definitions but also distinct differences. One difference, for example, is that Millon designates three personality disorders—the schizotypal, borderline, and paranoid—as the more severe personality disorders, while the other disorders are considered less severe. There is no such distinction in *DSM-III*.

There are two major strengths to this work. The first is the rich and detailed clinical description of the various disorders. The second is in providing a plausible theoretical framework into which to place the individual disorders. An 11-page chart describing and comparing the different personality disorders is provided at the end. The book has some weaknesses as well. Its attempts to talk about etiology and truncated discussions of development, genetics, and neurochemistry are so superficial as to be of little value. Also, Millon's approach of viewing all axis I disorders as epiphenomena of axis II disorders is not mainstream psychiatric theorizing.

Overall, however, the rich clinical description, organiza-

tion, and readability make this a good introduction for those who have not previously been exposed to the concept of personality disorders.

JAMES REICH, M.D., M.P.H.
Iowa City, Iowa

SCHIZOPHRENIA

Can Schizophrenia Be Localized in the Brain? edited by Nancy C. Andreasen, M.D., Ph.D. Washington, D.C., American Psychiatric Press, 1986, 87 pp., \$15.95.

This slender volume contains five brief chapters by participants in a symposium on cerebral localization of schizophrenia presented at the 1985 annual meeting of the American Psychiatric Association. The contributors are all psychiatrists. They apply the new technologies of brain imaging, computerized tomography (CAT scan), nuclear magnetic resonance (NMR), cerebral blood flow, and brain electrical activity mapping (BEAM) to the study of the brain in schizophrenia. Expressing, one hopes, an opinion not too widely held, Dr. Andreasen remarks in her introductory chapter that "because the brain looks a bit like the liver, we tend to think that it must behave a bit like the liver." As she and her coauthors go on to demonstrate, however, the highly differentiated anatomy and chemistry of the brain are most emphatically unlike the liver.

The new in vivo brain imaging techniques have generated a new excitement among psychiatrists and a welcome return to the anatomic studies that so occupied our neuropsychiatric predecessors. Drs. John Morihisa and Daniel Weinberger review their EEG and cerebral blood flow data favoring localization of schizophrenic pathology in the frontal lobes. Although the knowledgeable reader may find the evidence for frontal localization of the pathophysiology of schizophrenia somewhat less compelling than these authors do (particularly since the frontal EEG slowing they found may be largely eye movement and there is as yet no evidence of the decreased dopamine in frontal cortex on which their theory rests), their energetic search for causes is bound to be contagious. The excellent references will be very useful to newcomers to neuropsychiatry.

Dr. Andreasen follows with a chapter on the evidence for temporal lobe and limbic localization of schizophrenic pathology. She considers the relationship of schizophrenic speech and thought disorders to the aphasia and the role of D receptors in the development of "positive" and "negative" symptoms.

Henry Nasrallah asks, "Is schizophrenia a left hemisphere disease?" and, sagely, after reviewing the voluminous evidence pro and con, concludes with a lengthy bibliography that will allow interested readers to reach their own conclusions.

In a well-balanced chapter, Drs. Andrianne and Michael Reveley review their studies of cerebral ventricular size in monozygotic and dizygotic twins concordant and discordant for schizophrenia. They conclude that both genetic and environmental events act in concert to produce greater ventricular size in the affected twin.

Although one might wish that this small volume had been expanded to include some of the discussion that followed presentation of these papers, the monograph nevertheless serves its purpose well. Written in a clear, straightforward fashion, it provides a good introduction to current ideas and

research using new techniques of brain imaging to investigate schizophrenia.

JANICE R. STEVENS, M.D.
RICHARD SUDDATH, M.D.
Washington, D.C.

Research in the Schizophrenic Disorders: The Stanley R. Dean Award Lectures, vol. 1, edited by Robert Cancro and Stanley R. Dean. New York, SP Medical & Scientific Books, 1985, 287 pp., \$47.50.

Research in the Schizophrenic Disorders: The Stanley R. Dean Award Lectures, vol. 2, edited by Robert Cancro and Stanley R. Dean. New York, SP Medical & Scientific Books, 1985, 332 pp., \$57.50 (both volumes: \$95.00).

These two volumes contain the first 21 years' worth of the Stanley R. Dean Award lectures, featuring the collected works of the world's foremost schizophrenia researchers. This award, named in honor of Dr. Stanley Dean's important support for schizophrenia research, has been given annually since 1962 by the American College of Psychiatrists and the Fund for the Behavioral Sciences to an outstanding scientist in the field of schizophrenia research. It covers, therefore, all of the major developmental landmarks of the slow but rich and complex growth of schizophrenia research up to 1982. Although the work is addressed to the researcher and the serious student of this field, it is certainly also of interest for the clinician who treats schizophrenic patients and who wants to read these classical studies.

In addition to the historical perspective provided by these two volumes, I was confronted by two almost contradictory observations: on the one hand the field has seen a tremendous growth in new findings in the diagnostic, genetic, psychosocial, and biological spheres that have given us a much better understanding of this heterogeneous group of disorders; on the other hand, our understanding of specific causative mechanisms in the development of these disorders has not changed much over the past 25 years. Unfortunately, we are still dealing in this area with theories of schizophrenia, of which there are "as many as there are individuals who thought about the subject" (Cancro).

Volume 1 focuses on diagnosis and etiological theories, with a particular emphasis on psychosocial and family theories. Volume 2 presents research on cognitive and psychosocial factors as well as on biological and genetic factors in the schizophrenias. Many of the lectures are followed by a present-day comment by the award recipient covering some more recent developments in the recipient's particular area of interest, an interesting follow-up feature.

The historical perspective allows one the hindsight to review critically the different contributions and to see what findings have withstood the test of time. Leo Kanner's description of infantile autism and its relationship to schizophrenia remains a masterpiece, together with his prediction that specific syndromes would eventually be split off from the cluster of schizophrenia disorders. On the other hand, Gerard's vast study of the nosology of schizophrenia accumulated extensive measurements on phenomenological subgroups that remain of limited value without either biological correlates or an underlying conceptualization. The contribution of Carpenter, Strauss, and Bartko on diagnosis continues to be a major diagnostic tool and point of comparison for follow-up studies. Manfred Bleuler's major outcome re-

search still ranks high among the few long-term outcome studies. The studies of Mednick and Schulsinger on children at high risk for schizophrenia point to the importance of perinatal factors and to an interaction between genetics and perinatal casualty. The family studies of schizophrenia by Lidz and the related theory that emphasizes faulty family communications provide a valuable expansion of the egocentric thinking construct in family interactional patterns but retain an essentially taxonomic approach. Present-day family strategies that stress a psychoeducational model have certainly dropped this notion. Although Singer and Wynne's meticulous, controlled assessments of communication disturbances in schizophrenic patients' families confirmed the deviances in communicative styles noted by other observers, these findings have been somewhat replaced, at least in therapeutic approaches, by the construct of expressed emotion, derived from naturalistic observations in patients' homes.

Shakow's careful and elegant body of research on psychosocial deficits in schizophrenia and his resulting segmental set theory remains an important pathogenetic theory for the chronic forms of this disorder. The need for the schizophrenic patient to reintegrate the segmentalization of his set provides an excellent rationale for social skill learning interventions, which have been successful in the rehabilitation of chronic schizophrenic patients. Wing's contribution provides the empirical data and conceptual framework for the treatment of schizophrenic patients in the community. It is interesting to note that the therapeutic insights generated by this important body of work, which was published in the 1960s, only started to be applied in our large public facilities in the beginning of the 1980s. A significant amount of progress can be recognized in the biological sphere through the presentations of Kety, Carlsson, Snyder, and Axelrod, who retrace the uncertain beginnings of the recognition of specific catecholamines and their receptors in mediating the action of neuroleptic drugs and certain psychotic symptoms, culminating in the dopamine hypothesis. Finally, Wyatt introduces the possibility that, for a subgroup of patients, the dopaminergic system may not be diminished in function and may not be involved in their psychosis.

These are just a few of the many landmarks among the impressive wealth of data and conceptualizations contained in a well-organized fashion in these two volumes, reflecting our ever-increasing understanding of the "what" of the schizophrenic disorders. Our understanding of the "how" has to remain much more humble, as well as our ability to influence in a decisive manner the course of these devastating and often tragic disorders. The gap between what we know about these disorders and what we can do about them appears to grow with every new technological advance in the fields of neurochemistry, brain physiology, and brain-activity mapping techniques. I hope that this gap can be closed in the not too distant future.

JEAN-PIERRE LINDENMAYER, M.D.
New York, N.Y.

DEVELOPMENTAL DISORDERS

Handbook of Mental Illness in the Mentally Retarded, edited by Frank J. Menolascino, M.D., and Jack A. Stark, Ph.D. New York, Plenum, 1984, 437 pp., \$39.50.

Individuals who concurrently suffer from mental illness and mental retardation pose major problems to their fami-

lies, to the professionals who attend them, to their communities, and to the mental health and mental retardation care systems. This book focuses on the complex issues of this population. It is, therefore, a timely and welcome addition to the professional literature. We do not know either the exact incidence rate of mental illness in the mentally retarded population or the prevalence rate of both conditions in the same persons. The frequency of mental illness among the mentally retarded has been estimated to be as low as 5% and as high as 60%. The discrepancies result from several factors, as emphasized in this book.

I have visited many places, at times as an expert in child psychiatry and at other times as an expert in mental retardation. In practically every instance I am confronted with the same question: What is the best and most practical clinical plan for the half dozen or dozen individuals who do not fit the customary mold of mental retardation because of concomitant psychosis or severe emotional or behavioral problems? This situation has become increasingly acute during the last two and a half decades as deinstitutionalization programs have been implemented and responsibility for people with mental retardation and mental illness has been split among previously unified state agencies. This state of affairs is not the result of anyone's malicious intent. The movement of "separatism" brought with it a trend in professional education that insulated the two fields from each other. Today there are few experts versed in both conditions. I hope that this book will prove to be an added avenue for corrective rapprochement.

In five sections and 18 chapters the editors of this book deal with the nature of dual diagnosis, treatment and management interventions, special systems of services, training challenges, and research and future directions. As is the case with most edited books, the quality of the chapters is uneven. Some are indeed excellent, others are much weaker. Most readers will be able to discriminate among them either by their personal interests or by reading the initial pages of the chapters.

I was pleased with the focus in the book's title, mental illness in the mentally retarded, but was not overjoyed to find the term "dual diagnosis" in the title of the first section. Even though that term has become commonplace in professional jargon, it makes little conceptual sense. Why single out the concurrent presence of the two conditions for a designation of unique duality (1)? It would be equally logical to so identify a schizophrenic patient who in the process of aging also acquired some signs of senility.

Also troubling is the short shrift the relationship between autism and childhood schizophrenia on the one hand and mental retardation on the other received in the book. Although this complex phenomenon has occupied center stage between mental illness and mental retardation for several decades (2), it was essentially given only a small part of one chapter. It would have been interesting to read in greater detail the conceptual positions of the writers. Similarly, it was disappointing that attention to psychopharmacology or the use of psychotropics in mental retardation was limited to a mere 15 pages. This is one of the most controversial topics in mental retardation and mental health today.

Of occasional irritation were the following items. Mental retardation is at times described as a symptom and at other times as a syndrome. Some chapters are too repetitious. The section on training challenges very properly advocates the inclusion of topics on mental retardation in the preparation of mental health professionals. However, it would have been stimulating to read about other potential avenues for im-

provement as well—for example, the education of mental retardation professionals in mental health principles or the simultaneous use of experts in the two fields.

In spite of these probably idiosyncratic negative comments, I wish to emphasize the importance of this book. It is essential for those who work in the two fields, imperative for relevant libraries, and highly desirable for those who work with either mentally ill or mentally retarded persons.

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GEORGE TARJAN, M.D.
Los Angeles, Calif.

Attention Deficit Disorder: Identification, Course, and Rationale, by Lewis M. Bloomingdale. New York, SP Medical & Scientific Books, 1985, 159 pp., \$30.00.

In a recent publication, Weiss and Hechtman (1) indicated that 31 articles on the attention deficit disorder syndrome or its synonyms were published between 1957 and 1960. Between 1960 and 1975, more than 2,000 articles were published, and from 1977 to 1980, 700 articles were published. It seems that the literature has grown extensively since that time. Not only articles but book chapters and entire books are being written about the hyperactive child syndrome, the attention deficit disorder syndrome, the minimal brain dysfunction syndrome, and their different synonyms.

This book is the report of the second High Point Hospital Symposium on attention deficit disorder. It consists of nine chapters. Several of the chapters have to do with identification and diagnosis, a few with biochemical etiology and response to stimulant medication, two with follow-up data, and one with nonpharmacological interventions. For the most part, the authors of the various chapters are well respected investigators in the field. Following almost all chapters there is a summary of the discussion that occurred for each paper. Susan Campbell's work on hyperactive toddlers and Garfinkel and Klee's paper on adolescents with a history of childhood attention deficit disorder both present interesting data. Few data exist on the outcome of preschool children identified as hyperactive. Campbell has published on this subject elsewhere. The literature on the outcome of attention deficit disorder in adolescence has grown extensively and has been summarized by Weiss and Hechtman (1). Herb Quay presents a careful and lucid analysis of the relationships between aggression, conduct disorder, and attention problems and discusses the new revised Behavior Problem Checklist. Edelbrock also gives a nice discussion of ways of identifying the attention deficit disorder syndrome by rating scale data. Brown and colleagues summarize the existing biochemical literature available on the attention deficit disorder syndrome at the time of the symposium and tie this information in with pharmacological treatment.

In separate papers, Hicks and his colleagues and Kinsbourne talk about issues having to do with stimulant treatment, which remains the most popular treatment for this syndrome. Douglas discusses the clinical application of reinforcement intervention and the theoretical implications

of the response of children with this disorder to reinforcement.

The final paper deals with a screening test for "minimal brain disorder," the Sudden Interruption of Continuity (SIC) test. The results presented by these investigators are negative for children with this disorder in the age range that they studied.

Individual readers, depending on their interest, will find certain chapters in the book valuable reading. However, the most difficult thing for me, given the proliferation of literature on this syndrome, was to ascertain the major audience for the entire volume. It is not for those who are interested in a thorough review of the clinical picture, epidemiology, diagnosis, assessment, classification, outcome, and response to treatment. The book of Ross and Ross (2) would be better suited for this purpose. On the other hand, the clinician looking for a book that covers in detail diagnosis and treatment of this disorder from a multifaceted approach would not find this book satisfying either. For these purposes, Russ Barkley's book (3) is probably the best available at the present time.

An added problem in this manual is that much of the material presented by some of the authors has been published by them in journals and other books.

In summary, there are some interesting bits of information about the attention deficit disorder syndrome in this book. Investigators interested in studying a particular area will probably find the book most useful because one or two of the chapters may cover some of the newer aspects of areas that they are interested in investigating. The book cannot be recommended, however, as a textbook on the disorder, nor can it be recommended to the practicing clinician as one that will offer the most up-to-date practical ways of managing the disorder.

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DENNIS P. CANTWELL, M.D.
Los Angeles, Calif.

PSYCHOSOMATIC DISORDERS

Psychosomatic Illness Review, edited by Wilfred Dorfman, M.D., and Leo Cristofar. New York, Macmillan Publishing Co., 1985, 215 pp., \$29.95.

This book's editors are both central people in the publication of the journal *Psychosomatics*. Dr. Wilfred Dorfman is an elder statesman of the Academy of Psychosomatic Medicine and the founder and Editor-in-Chief of *Psychosomatics*, the Academy's official publication. Mr. Leo Cristofar is its editor. They tell us in the preface that it is composed of chapters which originally appeared as a series of review articles that, according to the book's copyright information, were published in 1982, 1983, and 1984 in *Psychosomatics*.

The volume consists of chapters covering a wide range of psychosomatic illnesses but missing some—most importantly, coronary artery disease, the single most intensively

researched illness in psychosomatic medicine. The preface states, "This volume provides authoritative, practical and up-to-date guidelines for managing patients." One might anticipate that such a statement would set one up for disappointment. This is not the case. The weakest part of the claim is that the material is up-to-date, which in any book would be hard to realize, no less a multiauthored one written over a period of 3 years. However, the book is authoritative and practical, which are its chief assets.

John J. Schwab's introduction gives a well-stated review of psychosomatic medicine and summarizes the contents of all of the 15 chapters. It is a job well done.

In his chapter on muscle-contraction (tension) headaches, Martin points out that headaches are a frequent symptom of depression but that the cause-and-effect relationship of depression and headache is unclear. In fact, studies have shown that most patients with muscle contraction headaches are not depressed. Raskin, writing on migraine, describes the similarity between tension and migraine headaches. Both occur predominantly in women, respond to amitriptyline and ergotamine-phenobarbital-belladonna medicine, and have an increased incidence of epilepsy. He points out, however, that, unlike tension headaches, migraine is a CNS disorder of vasomotor regulation and a systemic metabolic disorder. He discusses several prophylactic measures, including the use of propranolol and methysergide. He states that migraine is primarily not a psychogenic disorder and that people suffering from it appear to be under no greater stress than control subjects. Thus, he speaks of its not being a psychosomatic illness in the usual sense of the term.

Wolf's chapter on peptic ulcer gives the reader an excellent historical overview. However, this review is somewhat shy on most recent developments. Rosenbaum's report on ulcerative colitis is an excellent overview; he provides four case histories that add interesting clinical vignettes. Two of these are especially interesting: they include portions of an interview between the author and his patients. A chapter by Nadelson, Notman, and Ellis concerns psychosomatic aspects of obstetrics and gynecology. These authors describe psychological factors surrounding the menstrual cycle, pregnancy, childbirth, postpartum reactions, menopause, pelvic pain, and hysterectomy. They very succinctly summarize a most complex and underinvestigated area in psychosomatic medicine.

Sexual dysfunction in the medically ill is dealt with by Wise, who describes the biological bases of sexuality and covers well a wide group of sexual problems seen in physical illnesses. In the chapter on chronic pain, Webb discusses its historical perspective, the definition of pain, the biological influences on the pain experience, the differentiation between acute and chronic pain, the differentiation between organic as opposed to psychological chronic pain, and specific treatments. Concerning the latter, he tells us that most programs offer some combination of hypnosis-relaxation and cognitive manipulation to teach pain control. Modeling, which is the emulating of the behavior of another person, is a powerful means of learning and may be enhanced by videotapes. Biofeedback does not seem to offer any advantage over relaxation techniques. Other chapters deal with obesity, anorexia and bulimia, irritable bowel syndrome, essential hypertension, psychiatric effects of thyroid disturbance, diabetes mellitus, childhood asthma, and dermatological disorders.

This is an interesting book that concisely summarizes and reviews most major disease entities which belong under the category of psychosomatic medicine. It offers the reader a

practical overview of the treatment of patients with these illnesses. The chapters are written by individuals who, with few exceptions, are outstanding authorities in their respective areas. Excess verbiage is kept to a minimum, and one gets the impression that the originally edited articles were brought down to their leanest and most concise statements. This enhances the value of the book, especially to the beginner in the field. This book can also be recommended to general psychiatrists, medical students, nonpsychiatric physicians, and other professionals. Dorfman and Cristofar, along with the volume's authors, are to be congratulated for contributing to the production of a good book.

NORMAN B. LEVY, M.D.
Brooklyn, N.Y.

Psychosomatic Medicine and Liaison Psychiatry: Selected Papers, by Z.J. Lipowski. New York, Plenum, 1985, 446 pp., \$39.50.

Dr. Zbigniew Lipowski is one of the modern founders of consultation-liaison psychiatry. From 1959 to 1971, he directed the first consultation-liaison service in Canada at the Royal Victoria Hospital and the Montreal Neurological Institute. Throughout these early years, he was actively engaged teaching psychosomatic medicine, psychiatry, and psychiatric consultation at both graduate and undergraduate levels. In 1967-1968, he published his three-part review of "Consultation Psychiatry and Psychosomatic Medicine" in *Psychosomatic Medicine*. This work has served as the introduction to the teaching of consultation-liaison psychiatry throughout the world. These papers also serve as an "organizing principle" for this volume of his collected papers. Some of these have not been published before. Taken as a whole, this book emphasizes his major thesis that psychosomatic medicine and consultation-liaison psychiatry are two fields inextricably tied together. According to Lipowski, psychosomatic medicine has a broad scope, one encompassing a body of research and theory as well as a set of guidelines for medical practice. Consultation-liaison psychiatry embodies clinical applications of the psychosomatic approach to problems at the interface of psychiatry and medicine. The articles included in the collection trace the history of both fields and highlight the recent growth in all major aspects.

The book is divided into four parts. The first, covering theoretical concepts of psychosomatic medicine, begins with Lipowski's 1968 review of theoretical issues. It includes, among others, a 1981 paper entitled "Holistic-Medical Foundations of American Psychiatry: A Bicentennial" and "What Does the Word 'Psychosomatic' Really Mean?" published in 1984.

The second section deals with psychosocial reactions to physical illness. I found these previously unpublished papers to be exceptionally well written and very timely. In them Lipowski highlights the relevance of family issues and interactions in understanding patients' reactions to physical illness. The chapters review major theoretical concepts and representative studies in the areas of psychosocial reaction. Lipowski has found that the three core components of psychosocial reactions are the personal meaning of illness, the emotional responses elicited, and the modes of coping behavior. All three influence the patient's adjustment to illness as well as his or her response to medical advice and therapy. Therefore, the course and outcome of every illness

depend on how the patient evaluates the illness in subjective terms, responds to it emotionally, and copes with it. Although much of the work in this area remains speculative and descriptive, research that promises a significant development in the field is underway.

Part three deals with the complex relationship between physical disorders and psychiatric morbidity, which Lipowski believes is a neglected aspect of psychosomatic medicine that should be viewed as an integral part. This is an area straddling the boundaries of medicine and psychiatry that needs to be bridged. In this section are included many of Lipowski's original and carefully done studies on organic mental disorders and delirium. Particularly relevant is a 1983 paper on transient cognitive disorders in the elderly that highlights the role of consultation-liaison psychiatrists in diagnosing these organic states in an aging population. It has been estimated that in major medical centers between 50% and 60% of all consultations performed are on patients over

the age of 65. This percentage will only increase with the aging of the population.

The final section consists of articles on consultation-liaison psychiatry, beginning with a review published in 1967-1968. Other papers trace the development of the field during the past decade. This section provides a comprehensive overview and bibliography of the subject. I am supportive of the publication of this volume. It is a good thing to have these papers published together in a comprehensive manner and for easy reference by psychiatric residents, medical students, and students of all ages. Dr. Lipowski's work reasserts the indivisible unity of mind and body and keeps alive the finest traditions of the philosophers and physicians of antiquity. It is a treat to reread the papers previously published and a feast to read the new offerings.

ROBERT O. PASNAU, M.D.
Los Angeles, Calif.

Reprints of Book Forum reviews are not available.

Letters to the Editor

Delirium Induced by Verapamil

SIR: Calcium channel blockers are being explored for use in stabilizing affective illness, particularly bipolar disorder (1-4). We report here a case of delirious psychosis induced by a standard dose of verapamil hydrochloride given to a patient with bipolar disorder.

Ms. A, a 24-year-old single white woman, had suffered from bipolar I disorder since at least age 18. Before that, she had abused alcohol, marijuana, amphetamines, and LSD. She did not abuse alcohol or drugs after age 18, however, and her first manic episode (at age 21) was temporally related to the administration of a tricyclic antidepressant. She began to cycle rapidly the following year and, prior to her current hospitalization, had been hospitalized seven times and given a trial of all conventional therapies (except ECT) without success. She claimed to be "hypersensitive" to medications and had developed polyneuropathy while taking lithium, with a reduced creatinine clearance, and neutropenia while taking carbamazepine. Although the patient had attempted suicide several times, she had no history of hallucinations or disorientation.

The results of laboratory tests, physical and neurological examinations, and an EEG, given at the time of admission, were unremarkable. After a 3-week drug-washout period, during which her moods continued to cycle, Ms. A began a 3-week trial of partial sleep deprivation. She responded rapidly to this treatment, with a sustained hypomania that continued for a week after the trial was stopped. She was then started on a regimen of verapamil, 80 mg h.s., which was increased over the next 3 days to 240 mg/day in divided doses. The patient's cycling reemerged, however, and the verapamil was increased to 320 mg/day. Results of laboratory tests (CBC, thyroid function tests, and SMA-21) made on day 7 of the 320-mg dose of verapamil (about 3 weeks after the sleep deprivation trial) were unremarkable. That afternoon the patient, who had been suffering severe depression and psychomotor retardation for several days, suddenly began screaming in terror and ran away from the ward. When restrained by nurses, she continued to scream and attempted to bang her head and tear her hair. These symptoms cleared about 15 minutes after she was given chlorpromazine, 50 mg i.m., for sedation. She described auditory, visual, and tactile formicatory ("like things were crawling on me") hallucinations. She denied having had previous similar experiences.

Verapamil was discontinued for 2 days and then was reinstituted at 240 mg/day. Ms. A then developed a "heightened visual and auditory sensitivity," in which colors appeared brighter and sounds louder, which she reported had also preceded her delirium. The dose of verapamil was decreased to 160 mg/day and, with the addition of amitriptyline, 25 mg/day (for depression), the patient remained in remission for 6 months.

To our knowledge, this is the first report of a toxic delirium caused by a calcium channel blocker. Interestingly, this reaction occurred in an otherwise drug-free patient who was taking a standard dose of verapamil. Since the delirium occurred 3 weeks after cessation of partial sleep deprivation, it seems unlikely that they were related. It is unclear what relationship the patient's past drug exposure and adverse reactions to medications had to this toxic reaction.

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FREDERICK M. JACOBSEN, M.D., M.P.H.
DAVID A. SACK, M.D.
STEVEN P. JAMES, M.D.
Bethesda, Md.

Self-Inflicted Eye Injury

SIR: Although self-inflicted eye injury is rare, reports do exist of delirious and psychotic patients engaging in such behavior (1). Stinnett and Hollender (2) introduced to the literature in English the case of a patient with an obsessive-compulsive neurosis who blinded himself. They made a crucial distinction by noting that some authors have failed to recognize eye pressing as a mode of ocular injury separate from enucleation. We present here the case of a patient without psychosis or delirium who had an apparent obsessive-compulsive disorder (OCD) that manifested itself as an impulse to press on his eyes.

Mr. A, a 40-year-old white man, presented with a 23-year history of feeling a need to press on his eyes. Learned in combat, eye pressing served as a way for the patient to relieve anxiety. Over the decades, his self-mutilatory impulses had failed to be suppressed by chlorpromazine, thioridazine, haloperidol, perphenazine, imipramine, amitriptyline, or ECT. By the age of 40, Mr. A had damaged the vitreous bodies and retinas of his eyes so much that he was completely blind.

Diagnostically, he fulfilled the *DSM-III* criteria for an atypical impulse control disorder: failure to resist an impulse to perform an act harmful to himself, increasing tension before committing the act, and having an experience of release at the time of committing the act. Since the results of an EEG, tests for uric acid level and ceruloplasmin, CBC, sedimentation rate, thyroid function

tests, and SMA-20 were normal, there was no evidence of an organic etiology. Although self-destruction is seen in borderline personality disorder—a diagnosis given to Mr. A—the recurring impulse phenomenon did not fit with that category. Mr. A's recurring impulse to mutilate his eyes in the context of guilt suggests that his symptoms are best addressed under the rubric of obsessive-compulsive disorder. Having a recurrent ego-dystonic wish to hurt himself, the patient attempted to suppress the desire but often yielded to the self-destructive impulse. His blindness was a significant source of distress to him and severely impaired his social functioning. (His history of recurrent tics at age 10 is consistent with Green and Pitman's [3] observation that 11 of 16 obsessive-compulsive disorder patients whom they studied either had a history of tics themselves or had a family history of tics.)

To break Mr. A's cycle of anxiety and aggression leading to impulse leading to further anxiety, sedating doses of thioridazine and secobarbital were prescribed for 4 days. Two milligrams of pimozide in divided doses were then substituted for the thioridazine. Immediately the patient reported a decrease in the frequency of the impulses. With a dose of pimozide that eventually reached a total of 6 mg/day, Mr. A reported that the frequency of impulses to hurt himself had decreased from twice an hour to twice a day.

This patient and Stinnett and Hollender's patient regarded their disorder as a manifestation of a recurring impulse whose source they could not suppress. Both first exhibited compulsive behavior during childhood. Both described the impulse to press on their eyes in the context of guilt over past behavior. Even when they could resist the impulses, the obsessions were persistent. Interpretations offered to both patients did not help control the impulses. If further similar cases are eventually reported, it may be that this phenomenon will prove to be a distinct impulsive subtype of obsessive-compulsive disorder.

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DAN A. OREN, M.D.
NATHANIEL LAOR, M.D., PH.D.
New Haven, Conn.

Patient Incompetence in Legal Settings

SIR: I read with interest the article "Clinicians' Guidelines for Assessing and Presenting Subtle Forms of Patient Incompetence in Legal Settings" by Thomas G. Gutheil, M.D., and Harold Bursztajn, M.D. (August 1986 issue). Perhaps, of all the patients they describe, the paranoid patient poses the greatest challenge for the clinician attempting to assess competency. As they point out, the paranoid patient is often both articulate and persuasive in defending his or her point of view. The dividing line between paranoid ideation and so-called normal thinking is not always clear. In all but the

most extreme cases, surface plausibility may camouflage the irrational nature of the patient's underlying delusional distortions (1).

I would like to call attention to another index of incompetence in the paranoid patient that clinicians should consider: the diagnostic clue of "hypercompetency" (2). Hypercompetency (which was originally described in the context of competency to stand trial) is conceptualized as a defensive ego function whereby the paranoid patient attempts to cope with a suspected hostile environment. Such a patient exhibits an extensive knowledge of the legal process and thrives on adversarial conflicts with others (e.g., over the issue of refusing medication), zealously attempting to prevail over those perceived to be "against" him or her. With such patients, the clinician may find the following telltale clinical observations useful: 1) the patient is more concerned with legalistic and procedural niceties than with the substantive therapeutic issues at stake, 2) there is a conscious distortion of reality, and 3) there is a persistent although well disguised paranoid thinking disorder (2).

It should be impressed on the court that such patients are only "superficially competent"; that is, as a consequence of their paranoid distortions they have a factual but not a rational understanding of the relevant therapeutic issues. (It is my experience, however, that despite our best efforts, most courts will rule that such patients are competent because they possess a "modicum of competence.")

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ROBERT LLOYD GOLDSTEIN, M.D., J.D.
New York, N.Y.

Drs. Gutheil and Bursztajn Reply

SIR: Thanks are due Dr. Goldstein for his very relevant extension/elaboration of the competence issue with paranoid—especially litigious paranoid—patients. As he points out, the pragmatic issue often boils down to this: how *much* impairment of functional competence is *incompetence*? While judges' rulings are not predictable, the article was intended to give clinicians some assistance in making the "best case" on behalf of good care for their patients; to this task Dr. Goldstein's letter makes a valuable contribution.

THOMAS G. GUTHEIL, M.D.
HAROLD BURSZTAJN, M.D.
Boston, Mass.

Heroin-Induced Vomiting in Bulimia

SIR: Patients with bulimia use a variety of means to avoid the weight gain that would otherwise result from their binges. Behaviors such as vomiting, purging, fasting, and excessive exercise are commonly used and typically develop only after binge eating has become well established. Of these, vomiting appears to be the most frequent; it occurs in 74% of women who have bulimia (1). Vomiting is usually achieved by inducing a gag reflex with the fingers, although

some people are able to vomit without this maneuver. Recently, the use of the emetic ipecac by bulimic patients has been described (2).

I present here the unusual case of a young woman who developed bulimia after using heroin to induce vomiting.

Ms. A, a 28-year-old woman who was 163 cm tall, had been excessively concerned about her weight since early adolescence, when she weighed 51 kg. At the age of 13 she began to restrict her dietary intake severely (without vomiting) and reduced her weight to 44.5 kg for a period of 2 years. Between the ages of 15 and 17 she attempted to control her weight with appetite suppressants but was unable to reduce it below 54–57 kg.

In her early teens Ms. A had also begun to abuse various substances, particularly alcohol, stimulants, and benzodiazepines. After experimenting with heroin at the age of 17, she experienced marked nausea, which resulted in involuntary vomiting of a recent meal. As a consequence she began to use the emetic effect of the opiate deliberately to induce vomiting after meals, as a means of losing weight. This was in addition to her major use of the agent for its action as a euphoriant. Soon afterwards she developed a pattern of frequent binges (i.e., rapid consumption of large amounts of food during which she felt out of control) followed by heroin-induced vomiting to avoid weight gain. After 3 months she developed tolerance to both the emetic and euphoric effects of the opiate and began to induce vomiting manually after her binges, despite continuing frequent heroin use for the next 3 years. This pattern of more typical bulimia continued until she was referred to a clinic, when the binges and vomiting were occurring 30 times each week.

The association between bulimia and substance abuse has been well described; it is believed to reflect underlying difficulties with impulse control. This case demonstrates the development of bulimia in a woman with previously disturbed eating after the apparently serendipitous discovery of heroin as a means of inducing vomiting. The disorder persisted despite the development of tolerance to the opiate. This case is important in highlighting a previously undescribed means of facilitating bulimia. It also suggests another possible reason for the association between bulimia and substance abuse.

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PHILIP MITCHELL, M.B., B.S., M.R.C.PSYCH.,
M.R.A.N.Z.C.P.
Little Bay, N.S.W., Australia

Unexpected Consequence of Treatment for Attention Deficit Disorder

SIR: The frequent occurrence of attention deficit disorder, residual type, among young adult men admitted to chemical dependency units has been reported by Wood et al. (1). The following is a report of an unexpected consequence of treating a patient with this diagnosis in an inpatient program. To our knowledge this is the first instance in which the

diagnosis of attention deficit disorder entered into a court judgment in a criminal case.

At his own request, Mr. A, a 19-year-old man with marijuana addiction, was admitted to the chemical dependency treatment unit of a state hospital. He showed no progress in treatment and had difficulty complying with house rules despite his apparent commitment to the program. The clinical diagnosis of attention deficit disorder was made on the basis of clinical history and neuropsychological testing. The patient was started on pemoline, 37.5 mg/day, and showed remarkable improvement in his ability to follow the program material and to incorporate treatment goals into his life style. A drug holiday confirmed the benefit of medication: the symptoms seen prior to pemoline treatment all returned when pemoline was withheld. Symptoms again remitted when pemoline was restarted.

During treatment, Mr. A acknowledged his involvement in a burglary; he reported his involvement in this previously unresolved crime to the authorities. At the time of his discharge from the chemical dependency unit, he was remanded to jail to await trial. As requested by his attorney, the chemical dependency unit physician submitted a deposition regarding the patient's past history, his course of treatment, and the nature of attention deficit disorder. The follow-up recommendations given in the deposition were ordered by the court; they included further evaluation of the patient by a psychiatrist and transfer to a halfway house.

To our knowledge, this is the first reported case in which the diagnosis of attention deficit disorder, residual type, has been considered in the disposition of a criminal case. The wisdom of the court in this case has been confirmed. This young man, who had a handicap that was not visible and who probably never would have succeeded in life, is now showing great potential for making an above-average contribution to society.

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ROBERT D. MERRILL, M.D.
St. Peter, Minn.
BARRY GARFINKEL, M.D.
Minneapolis, Minn.

Doses and Blood Levels of Tricyclic Antidepressants

SIR: It is widely believed that there is little possibility of additional therapeutic benefit to be derived from raising the dose of imipramine or similar tricyclic antidepressants beyond 300 mg/day or raising the blood level beyond 250 ng/ml. Clinicians who hold this opinion change the medication rather than increase imipramine above these levels.

An APA task force report (1) on blood levels of antidepressants supported this belief. It states that blood levels of imipramine beyond 250 ng/ml can produce more side effects but produced no change in antidepressant response of patients in five of six studies.

We report two cases of patients who required doses

beyond these ranges to achieve a favorable antidepressant response.

Ms. A, a 30-year-old woman, presented with major depression, according to *DSM-III* criteria, of 30 weeks' duration. Her symptoms included hypersomnia, overeating, mood reactivity, daily panic attacks, and agoraphobia. She was treated with imipramine in increasing doses over a period of 48 weeks. At a dose of 350 mg/day (combined blood level of imipramine and desipramine = 375 ng/ml), after 5 weeks her depressed mood was still present, her panic attacks were still occurring, and she was agoraphobic. Her dose of imipramine was increased to 500 mg/day by 8 weeks (combined blood level = 620 ng/ml), with good remission of her symptoms. She continued to take 500 mg/day of imipramine for 35 weeks. During the course of treatment her dose was decreased three times. At 450 mg, her combined blood level of imipramine and desipramine was 474 ng/ml. Each time there was a decrease, she had a return of depressive and agoraphobic symptoms.

Ms. B, a 46-year-old woman, had recurrent major depression, bipolar II disorder, panic attacks, and agoraphobia. She required 300 mg/day of imipramine (blood level = 90 ng/ml) for 10 weeks to obtain a complete remission. She was switched to nortriptyline because of the side effects she experienced with imipramine. At a dose of 100 mg/day of nortriptyline, she was not housebound but was still moderately depressed. At a dose of 275 mg of nortriptyline (blood level = 175 ng/ml), she was "superb, 100% better." When the dose of nortriptyline was reduced to 150 mg/day, there was a return of depressive symptoms. Raising the dose to 275 mg/day brought relief of depression.

Imipramine and nortriptyline levels in these two patients were assayed by gas-liquid chromatography with a nitrogen-phosphorous detector operated in the nitrogen mode (2, 3). The intra-assay and interassay coefficients of variation were <6% and <8%, respectively, for the tricyclic antidepressant drug and metabolites.

It seems that the rule for blood levels and doses of tricyclic antidepressants may be correct on the average but that occasionally, as shown by these two cases, patients who do not benefit from lower levels do benefit from higher doses or blood levels than are usually recommended. When the doses of tricyclic antidepressants were decreased in these two patients, they had recurrences of depression; thus, it was necessary to maintain them at higher levels. While these cases suggest that higher-than-usual plasma levels of imipramine and nortriptyline can be beneficial, further information and a prospective study are necessary before any clinical conclusions can be drawn. Doses and blood levels higher than those usually recommended should be tried in carefully selected patients and should not be used routinely.

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CAROL W. BERMAN, M.D.
PATRICK J. MCGRATH, M.D.
JONATHAN W. STEWART, M.D.
New York, N.Y.

Potentiation of Propoxyphene by Phenelzine

SIR: Interactions between monoamine oxidase inhibitors (MAOIs) and the narcotic analgesic meperidine have been noted for some years (1) and have led to warnings against their concomitant use. Although studies in animals have shown that narcotics increase in potency in the presence of MAOIs (2), to my knowledge clinical reports of this same phenomenon, with the exception of reports on meperidine, are lacking. I report here a case in which phenelzine apparently led to an increase in the effect of propoxyphene but did not produce serious toxicity.

Ms. A, a 55-year-old white woman with a 5-year history of depression and panic attacks, also experienced intermittent but moderately severe back pain and took propoxyphene, 100 mg, plus acetaminophen, 650 mg, for relief. She had been treated at a mental health center with doxepin, trazodone, amitriptyline, and alprazolam, but because of continued depressive symptoms and worsening panic attacks (daily) she was referred for consultation.

She was quite depressed but was more upset about her panic attacks. She was on estrogen replacement therapy and, shortly after I saw her, began taking propranolol, 20 mg t.i.d., for treatment of essential tremor. Propranolol, which has been associated with inducing depression (3), did not affect her mood. I decided to treat her with phenelzine, 30 mg twice daily, because of recent reports that phenelzine may be particularly effective in patients with a combination of depression and panic attacks (4). Within 2-3 weeks Ms. A experienced a dramatic improvement in both her depression and her panic attacks.

While taking phenelzine Ms. A experienced a recurrence of back pain and took her usual doses of propoxyphene and acetaminophen. Within 2 hours she described feeling very sedated and groggy and had to lie down. This state lasted about 1 hour, and she experienced it as unpleasant. During this time she denied any changes in breathing, temperature, or heart rate and did not experience headache or neuromuscular problems. Because this reaction was so unusual, Ms. A thought that it was caused by something other than propoxyphene/acetaminophen. Therefore, several days later she took a second dose, but she experienced another reaction identical to the first. She called me and I advised her to try acetaminophen alone, which she did without any problem.

To my knowledge, this is the first clinical report of enhanced propoxyphene effect in a patient taking an MAOI. Several points are worth mentioning. First, this reaction was probably not medically serious, although in the absence of a physical examination this assumption must be tentative. Second, the symptoms described could be related to an enhanced effect of expected propoxyphene properties—sedation and somnolence—rather than to the emergence of unexpected effects such as hyperthermia, agitation, and

hyperreflexia, which have been reported with MAOI-meperidine interactions (1). My observations in the case of Ms. A are therefore compatible with results of animal studies that have demonstrated an increase in the potency of narcotics in the presence of MAOIs (2). The principal clinical indications, as previously noted by Meyer and Halfin (1), are to avoid the use of narcotics by patients taking MAOIs but, if narcotics are needed, to use low dosages, avoid meperidine, and monitor for side effects or an increase in the potency of the narcotics.

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JAMES C. GARBUTT, M.D.
Chapel Hill, N.C.

Sympathomimetic-Induced Depression

SIR: I report here two cases of major depression that were possibly caused by the use of a commonly prescribed decongestant medication, phenylpropanolamine hydrochloride with chlorpheniramine maleate (Ornade). In both cases, the patient had no history of depression, nor was there a recurrence of depression after discontinuation of the drug.

Psychotic reactions to sympathomimetics, although rare, are reported in the medical literature. The reactions include schizophrenia (1, 2), paranoid psychosis with visual and auditory hallucinations (2, 3), secondary mania (4), and acute psychotic syndrome (2, 5). An extensive search of the literature, the manufacturer's files, and records from the Food and Drug Administration did not yield any reports of major depression associated with any of these agents.

Mr. A, a 32-year-old man, began using phenylpropanolamine hydrochloride for relief from the symptoms of hay fever. Within a few weeks, he noted lack of motivation, loss of appetite, early morning awakening, and, finally, some suicidal thoughts. These symptoms persisted for 4 weeks. While arranging for psychiatric consultation, he entertained the thought that the depression might be induced by medication; upon discontinuation of the drug, all symptoms remitted. Mr. A was in the middle of a psychiatric residency, was knowledgeable about the symptoms of depression, and had undergone routine medical evaluation, with no abnormal findings.

Mr. B, a 44-year-old man, reported loss of libido, early morning awakening, and generally depressed affect. These symptoms had been present for nearly a year. He denied using any medications. When he sought psychiatric consultation, amitriptyline, 50 mg h.s., was prescribed, and the dose was gradually increased to 150 mg h.s. After 4 weeks at the higher dosage, Mr. B reported a minimal change in affect and no sleep disorder, but there was no

return of libido. A blood level determination showed the concentration of amitriptyline to be 175 ng/ml (within the therapeutic range).

When there was no response after 2 more weeks, the psychiatrist decided to change to a monoamine oxidase inhibitor. He advised Mr. B about the necessary dietary restrictions and also instructed him not to use any medications without consulting him first. At this point the patient asked whether he should discontinue his sinus medication, which led to the revelation that he had been using phenylpropanolamine hydrochloride for about the same period of time that his depressive symptoms had been present. Discontinuation of the drug, without the addition of any antidepressant medication, led to complete disappearance of all the depressive symptoms.

It is logical to assume that phenylpropanolamine hydrochloride was the causative agent in the depressions described. This underscores the need for the physician to know all medications a patient is taking when evaluating or treating psychiatric disorders. It is also important to remember that the agent probably implicated in these two case reports and in others in the literature is available in many over-the-counter and prescription preparations for use as diet aids and cold remedies. Some use of over-the-counter medications may not be reported to physicians unless there is deliberate probing. It is clear from most reports that the use of sympathomimetics does not need to be at overdose levels to produce adverse reactions.

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BENZION TWERSKI, PH.D.
Pittsburgh, Pa.

Classification and Diagnosis

SIR: As we improve our skills in assigning patients to diagnostic classes, it is important that we not lessen our skills in diagnosis. It may seem paradoxical that this could happen, but there are some fundamental differences between classification and diagnosis. It is a truism of taxonomy that the individual is not classified but is placed in a classification, and *DSM-III* states that it is a "misconception" to think that a classification of mental disorders classifies individuals. Thus, we can see that placing a patient in a class, and more specifically a "diagnostic class," can be one act of diagnosis but is not necessarily the whole thing. This is obviously what *DSM-III* is aiming at with its axes II-V. These axes deal with characteristics of the individual that may not be shared by other members of the class designated on axis I. The extent to which these individual characteristics can be made systematic and the usefulness of doing so are matters for debate

and trial. It is worth reminding ourselves that when we deal with diagnosis in the comprehensive sense, we are typically dealing with an individual, and we have the liberty of using a sentence or even a paragraph.

My concern about this matter arises from observing the responses of psychiatric residents and medical students when they are presented with clinical information about a patient. When asked to express his or her assessment of a patient, the resident or student will frequently say something like, "This patient has an affective disorder." The silence that then ensues implies that there is nothing more to say. I do not usually disagree with the diagnostic class selected; I disagree with stopping at that. Something more comprehensive is needed.

If I take my nonfunctioning automobile to a mechanic and ask, "What's your diagnosis?" and he says, "It doesn't run," I am not satisfied. The automobile has been placed in a classification of nonfunctioning vehicles, but I want something more: some idea of what the trouble is and, if possible, some idea of how it got that way and what it might take to fix it. In similar fashion, if we consider the patient with an affective disorder, we may add as part of the diagnosis that she is miserable because her husband has Alzheimer's disease, and she wants someone to take care of her the way she has to take care of him. The important information could be made formal on axes II and IV or, when dealing only with an individual, be simply stated, as above, in a descriptive sentence. The important thing, in the true meaning of the word "diagnosis," is to be comprehensive.

MYRON G. SANDIFER, M.D.
Lexington, Ky.

More on Posttraumatic Stress Disorder

SIR: Laufer, Brett, and Gallops (1) suggested that the symptoms of posttraumatic stress disorder are usefully conceptualized as two distinct subtypes for Vietnam veterans who were exposed to different kinds of trauma in combat. However, the authors gave no evidence for the internal consistency of the "reexperiencing" and "denial" subscales they created, or evidence about the differential patterning of the symptoms, in support of their claim of two distinct subtypes. (Similarly, the authors did not cite any evidence of reliability for the two independent scales they developed: "Exposure" and "Participation.") Further, it is incorrect to attribute a significant difference between two regression coefficients to the fact that only one reaches significance. The hypothesis that the coefficients are the same must be directly tested. Without an underlying structure, these apparent findings are, in any case, unlikely to be reproduced.

Using the same data set as Laufer et al., we found a matrix of correlations of the posttraumatic stress disorder symptoms to be relatively uniform (and low); no set of symptoms stood out as a separate cluster. Second, no factor analytic model with one, two, or more factors fitted the data (as determined by a maximum likelihood method). This was true for a factor analysis based on tetrachoric correlations, the appropriate method for dichotomous items, as well as for a factor analysis based on the more conventional Pearson *r*. Third, no cluster analysis or multidimensional scaling bore any relation to the scheme proposed by Dr. Laufer and associates. At best, clustering and multidimensional scaling suggested a few outlier items and a single-dimensioned core. The only model which fitted these data is a latent class model

with three classes but a single dimension for the posttraumatic stress disorder symptoms.

Analysis of these data with the addition of a few more indicators of posttraumatic stress disorder (2, 3) suggests differences in the patterning and prevalence of symptoms between acute and chronic states. Immediate or acute reactions to a traumatic stressor are characterized by more subdued symptoms like loss of interest and depression. As the reaction becomes chronic, symptoms such as hyperalertness and intrusive recollections of the trauma predominate, although the other symptoms are also present.

Laufer et al. maintained that their table 3 showed that posttraumatic stress disorder is more associated with other variables than with traumatic war experiences, yet combat and witnessing and participating in abusive violence referred to events in Vietnam. The other variables in the table—demoralization, guilt, arrests, and substance abuse—occurred after the Vietnam experience, along with the symptoms of posttraumatic stress disorder. Association between the latter variables and posttraumatic stress disorder thus may have occurred because they are all consequences of Vietnam experiences such as combat. Correlations between symptoms measuring the consequences of Vietnam and posttraumatic stress disorder must include controls for the experience in Vietnam. Otherwise, readers might misinterpret table 3 to mean that posttraumatic stress disorder symptoms are no more likely to be caused by combat than by substance abuse or feelings of guilt. Boulanger and Kadushin (4) demonstrated an interactive effect: substance use and violent behavior, among other factors, are increased by the presence of posttraumatic stress disorder that has resulted from exposure to combat.

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CHARLES KADUSHIN, PH.D.
GHISLAINE BOULANGER, PH.D.
New York, N.Y.

SIR: While attempting to study the vivid autobiographical memories of nonpsychiatric outpatient veterans, we unexpectedly found that some veterans cried during the interview. Veterans who reported seeing combat in World War II, Korea, or Vietnam were more likely than those who had not seen combat to cry when asked to describe "the clearest memory" from their past or when asked the seemingly benign questions "Were you on active duty?" and "Did you actually see combat?" It was also found that people who cried had not talked about their vivid memories as many times as those who did not cry. Furthermore, the people who cried and had seen combat often stated that they "tried not to think about their war experiences."

Of the 27 patients we surveyed, none had a history of

psychiatric illness. Ten had seen combat: eight in World War II, one in Korea, and one in Vietnam. Five veterans cried while answering the questionnaire. The trend for the veterans who cried was not to talk in their private lives about their war experiences. This avoidance pattern seems to be a milder, subclinical form of the denial symptoms experienced by the Vietnam veterans studied by Laufer, Brett, and Gallops (1).

On the other hand, there were five veterans who had seen combat and did not cry when discussing their war experiences. It is interesting to look at the conditions that seem to have protected them from crying. One patient had been a prisoner of war in Germany for 2 years. He said that he had not talked about the war for 6 or 7 years after he came home; it made him sick to think about it. Then he "got it out, and it was bad for a while." Now he can talk about it, and he goes to annual state and national meetings of former prisoners of war. Another patient was a tailgunner in a B-29 in the South Pacific during the air offensive against Japan. He never knew whether he had actually killed anyone. A third patient had a history of head injury, and now his memory is so poor that he does not remember the war clearly. The fourth patient described himself as "always being lucky" and stated that he has talked with his brother about the war "hundreds of times." The fifth patient, a parachuter in World War II, was a prisoner of war for a short time. He has talked about his war experiences "hundreds of times" and states that he "uses alcohol to try to forget things."

The protecting factor in our study seemed to be the frequency of talking about war experiences. A multivariate analysis of variance that used 15 variables related to the vivid memory and the patients' characteristics revealed that talking was significantly related to whether the patient cried or not ($F=8.96$, $df=1,25$, $p=.006$). This was the only significant factor we found. These results point to the need for further study of the effects of war on veterans who served in World War II and Korea as well as those who served in Vietnam.

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PAMELA POE PEPPER, M.ED.
HERBERT F. CROVITZ, PH.D.
Durham, N.C.

Borderline Personality and *DSM-III*

SIR: Those who resist borderline personality's going the way of cyclothymic personality—reclassification as an affective disorder—have a legitimate concern, for where are the patients with a cyclothymic personality now? According to *DSM-III*, they are dead, gone, and reincarnated, because saying someone has a cyclothymic affective disorder just isn't the same as saying he or she has a cyclothymic personality. And so clinicians who know that patients with a borderline personality do exist have a reasonable fear that any reclassification would be murder.

Why did the developers of *DSM-III* think that if cyclothymia is an affective disorder it is no longer a personality disorder? The assumption must have been that personality disorders are entities in their own right and can exist without cognitive, affective, or anxiety disorder. If this

assumption were true, then *DSM-III*'s either/or position would make sense, and when cyclothymic personalities are found to have an affective disorder, cyclothymic personality ceases to exist. But the continuing existence of real, live people whose personalities, and not just their moods, go through cyclothymic changes reduces that assumption to absurdity.

In other words, if cyclothymia is considered to be a form of bipolar affective disorder, then cyclothymic personality should be listed under bipolar disorders, and the same would hold for borderline personality. Indeed, as soon as the understanding of each personality disorder matures sufficiently, it should be listed with the appropriate group of cognitive, affective, or anxiety disorders without losing its personality, either in name or in spirit.

In this way, we will neither kill the concept of personality disorder nor take the illogical position that a personality can be disordered without there being a disorder in one of the primary components of personality (cognition and affect).

KENNETH A. NAKDIMEN, M.D.
New York, N.Y.

Sexual Side Effects of Alprazolam

SIR: We read with interest two recent reports regarding the sexual side effects of alprazolam (1, 2). A number of patients receiving alprazolam in our anxiety disorders program reported a change in sexual functioning while they were taking the medication for panic disorder. Patients in this program were receiving dosages of alprazolam ranging from 3 to 10 mg/day in divided doses. We report here the findings of a survey of changes in sexual functioning in patients who had been treated with alprazolam for several weeks.

We asked the patients to compare their predrug level of sexual functioning and various aspects of their functioning after several weeks of alprazolam treatment by rating on a 10-point scale their levels of libido (sex drive), ability to achieve orgasm, and (men only) ability to achieve and maintain erections. A score of 5 indicated no change, 0 indicated much worse, and 10 indicated much better.

Thirty-two patients responded to our questionnaire. Thirteen patients indicated no change in the level of their libido (rating of 5); 15 indicated decreased libido (rating of 0 by five patients, 1 by three patients, 2 by two patients, 3 by two patients, and 4 by three patients); four patients reported improvement in sex drive (rating of 10 by two patients, 8 by one patient, and 7 by one patient). Ability to achieve orgasm was rated as unchanged by 11 patients; 16 patients rated themselves as worse (rating of 0 by eight patients, 1 by four patients, 2 by one patient, 3 by one patient, and 4 by two patients). Three patients noted improvement (rating of 10 by one patient, 8 by one patient, and 7 by one patient). Two patients failed to respond to this question. Of the nine men who responded to the question about erectile function, five reported no change and four reported a decrease in function (rating of 3 by two patients, 2 by one patient, and 0 by one patient). The last patient was anorgasmic and unable to achieve erection.

These data support the contention that alprazolam treatment may be associated with a decline in sexual functioning in some patients. The majority of our patients experienced adverse effects, although it is interesting that a small number of patients enjoyed an increase in their sexual functioning after receiving alprazolam.

Since the data were collected in an open fashion, with the use of nonstandardized ratings, these preliminary findings should be viewed cautiously. Our clinical experience suggests that reduction of dosage or switching to a different medication is usually helpful in reducing or reversing unwanted sexual side effects. These findings should be confirmed by the use of standardized ratings under placebo-controlled, double-blind prospective conditions.

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R. BRUCE LYDIARD, PH.D., M.D.
ELIZABETH F. HOWELL, M.D.
MICHELE T. LARAIA, R.N., M.S.N.
JAMES C. BALLENGER, M.D.
Charleston, S.C.

Nicotine and Panic Attacks

SIR: We would like to comment on two letters published in the *Journal*: "Can Nicotine Control Panic Attacks?" by Lewis Brodsky, M.D., (April 1985 issue) and "Nicotine Gum to Treat Panic Attacks?" by John R. Hughes, M.D. (February 1986 issue). Both authors appeared to suggest that nicotine may possess antipanic properties and thus may be a useful therapeutic agent for panic attacks.

Extensive animal studies have demonstrated that the pharmacological effects of nicotine depend on the baseline arousal level of the organism (1). Nicotine may provide stimulant properties when the baseline arousal level is low, whereas sedative activity with reverse effects may be observed if the arousal level is high. Thus, if excessive cigarette smoking exerts any antipanic effect at all, it probably results from nicotine's sedative effect. In studies of nicotine's subjective effects on human beings, nicotine has consistently been shown to be a euphoriant. When human subjects who had been given intravenous nicotine were asked to identify the substance in the injection from a list of commonly used drugs, the most common misidentification was cocaine, followed by morphine (2). This finding is comparable to that obtained in animal drug discrimination studies (3). Tolerance to the sedative effects of nicotine will quickly develop, and in chronic tobacco abusers, nicotine exerts its main effect through its stimulating properties (4).

To achieve a constant high plasma level of nicotine, one must maintain a state of heavy smoking or chew nicotine gum at regular intervals. Thus, we feel that the role of nicotine in treating panic disorders is limited. Its efficacy would probably relate to its sedative effects, which disappear with the development of tolerance. Its side effects, especially if the nicotine is obtained through smoking, would far outweigh its advantages.

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IRADJ MAANY, M.D.
GEORGE WOODY, M.D.
EDWARD FOULKS, M.D., PH.D.
Philadelphia, Pa.

Dr. Hughes Replies

SIR: Drs. Maany, Woody, and Foulks believe that nicotine may not be useful in treating panic attacks because patients might develop tolerance and dependence. They state that tolerance develops to the "sedative" effects of nicotine. The references they cite are animal studies which show that tolerance develops to nicotine-induced depression of motor activity and contingent responding. Several more specific measures of anxiety reduction in animals are available, e.g., increases in behavior that is being punished. Nicotine does act as an anxiolytic in such circumstances (1). Tolerance has not been reported in these measures, and in fact, one study reported sensitization (2).

Dr. Maany and colleagues suggest that nicotine treatment could produce dependence. I agree; however, several factors may make dependence unlikely. For example, although nicotine obtained through cigarette smoking can produce dependence among smokers, whether this is true with products that deliver a low, gradual dose of nicotine and whether it is true among nonsmokers is unclear. For example, in a recent study, my colleagues and I found that after repeated doses, nonsmokers and long-abstinent former smokers rated nicotine gum as aversive and preferred placebo to nicotine (paper presented at the annual meeting of the American Psychological Association, Washington, D.C., August 1986).

In their last sentence, the authors imply that I am suggesting cigarettes as a therapeutic drug. This is not so. Rather, I was considering the possibility of using one of several new routes of delivering nicotine alone, e.g., gum, patch (3), and nasal solution (4).

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JOHN R. HUGHES, M.D.
Burlington, Vt.

ECT Results and Meta-Analysis

SIR: The evidence on which Janicak et al. (1) base their claim of ECT's "clear superiority" over other forms of

treatment for severe depression is insufficient to substantiate so broad a conclusion. Important questions can be raised concerning both their analytic procedures and their selection of studies for consideration.

In the comparison of ECT with simulated ECT, the authors examined the results of six studies, four of which were conducted 20 or more years ago. At the same time, more recent studies (2–5)—conducted, in fact, specifically because previous investigations were thought to be methodologically flawed—were not considered. Had these studies been included, a different pattern of results would have emerged. There was a trend for patients who received ECT to be less depressed at the end of the formal treatment regimen than their counterparts who received simulated ECT. (The regimen generally consisted of approximately six treatment sessions over the course of 2 or 3 weeks.) However, in each study the differences between patients who had real ECT and patients who had simulated ECT had disappeared within 2–3 months after the treatment regimen. The typical explanation given was that after the initial regimen, patients were treated as the attending clinicians saw fit, which meant that many of the patients who had been in the simulated condition received ECT. However, while it is true that this might have accounted for the gradual convergence of results in the two groups, the results could be equally well explained by the interpretation that ECT is no more effective than simulated ECT in terms of long-term changes in depressive symptoms. Particularly because the authors of these studies did not present statistics concerning improvement rates among those patients in the simulated condition who did and did not receive subsequent ECT, there is no basis for choosing the former explanation. The justification generally given for later administering ECT to patients who are in the simulated condition is that it would be unethical to withhold a potentially beneficial treatment. The circularity of this, however, is that it presupposes the efficacy of the procedure being tested and simultaneously prevents the very evidence that would be necessary to justify this conclusion from being obtained. The net conclusion is that at the present time, no clear empirical evidence exists that 6 weeks after treatment patients who receive ECT are any different from those who do not.

Important questions also need to be asked concerning the use of meta-analysis to address an issue of this kind. Meta-analysis is not yet the exact science its proponents would have us believe. For example, what impact does the fact that positive findings are more likely to be published than negative findings have on a study of this kind? Such a question cannot be merely ignored. In the coming years we will almost certainly see methodological refinements in these procedures which address many of the criticisms that can currently be made. However, at the present time, the results of any such attempt to quantitatively summarize the results of many different experimental findings must be viewed with a healthy degree of skepticism. Meta-analysis may be useful as a means of clarifying what the basic questions are in a particular area, but to base clinical decisions of any importance primarily on their results would be potentially irresponsible and clearly unscientific.

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JOHN S. UEBERSAX, PH.D.
Durham, N.C.

Drs. Janicak and Davis Reply

SIR: We seriously question Dr. Uebersax's letter commenting on our meta-analysis of ECT results. Of the four recent studies he lists to refute our findings (his references 2–5), Gregory et al. had not been published at the time our article appeared; while the other studies were available, we specifically stated in our Method and Discussion sections that the presentation of data was such that we could not extrapolate each patient's response in order to include it as part of the meta-analysis. Although we cannot perform a meta-analysis based on the raw data of these more recent studies, a simple inspection reveals that 1) Brandon et al. found real ECT superior to simulated ECT ($p=.00005$), Gregory et al. found real ECT superior to simulated ECT ($p<.001$), Johnstone et al. found real ECT superior to simulated ECT ($F=7.8$, $df=1,54$, $p<.007$), and Freeman et al., who compared two real ECTs to two simulated ECTs, found real ECT superior ($p<.05$). If we combine the individual probabilities from these four studies by the method of Fisher (1), we find that real ECT is superior to sham ECT at $p<.00000007$. This is quite comparable to the results of our meta-analysis, which also found real ECT superior to simulated ECT ($p=.000003$). Dr. Uebersax claims that "had these studies been included, a different pattern of results would have emerged." Our inspection of these data indicates that the outcome would have been the same.

Further, most patients in these recent studies who initially received simulated ECT subsequently received real ECT and/or tricyclics. This makes conclusions about the comparative long-term benefits of real and simulated ECT impossible.

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PHILIP G. JANICAK, M.D.
JOHN M. DAVIS, M.D.
Chicago, Ill.

Comment on the Review of *The Foundations of Psychoanalysis*

SIR: I was very disappointed in the review by Nathaniel Laor, M.D., of Adolf Grünbaum's *The Foundations of Psychoanalysis: A Philosophical Critique* (July 1986 issue). Grünbaum's book is far more important, provoking, and intelligent than the review indicated.

Essentially, Grünbaum argues against Popper's contention that psychoanalysis is unscientific because its tenets cannot be submitted to experimental investigation. Popper's ideas

justified the school of thought known as hermeneutics, according to which psychoanalysis can be considered as a closed system, immune from application of the scientific method.

This view is devastating to psychoanalysis because it would place it forever outside the realm of science and medicine. In a brilliant but complex argument, Grünbaum demonstrates that Popper is largely incorrect; the assertions and principles of psychoanalysis can definitely be formulated into scientifically testable hypotheses. This should be good news to most academic and practicing psychoanalysts, who very much hope that their method of treating psychiatric patients can be shown to be systematically helpful.

Dr. Laor implies that Grünbaum cannot possibly address these issues because he is not a psychoanalyst himself and therefore only has access to what psychoanalysts say they do rather than to what they actually do. This is dangerous criticism on two grounds. First, it implies that only psychoanalysts can usefully speculate on the scientific relevance of psychoanalysis. I hope that this is not a view shared by most psychoanalysts, who have welcomed the comments of intelligent people from a variety of academic disciplines since the time of Freud. The criticism is also entirely irrelevant to Grünbaum's work; the issue is whether any of the organized principles and tenets of psychoanalysis are testable by the standard scientific method.

It is true that Grünbaum occasionally asserts that some psychoanalytic notions are scientifically invalid or that he predicts they would be rendered invalid if studied scientifically. This may create the impression that the book is hostile to psychoanalysis. What Grünbaum's private opinion of psychoanalysis is I do not know, but the book is not in any way an attack on psychoanalysis. Rather, it is a difficult and technical attempt to show how psychoanalysis can usefully be studied. The book will be difficult for readers inexperienced in technical philosophical discourse, but it is well worth the effort. Psychoanalysts—and, indeed, scientists of all disciplines who are interested in mental health research—should welcome this outstanding contribution.

JACK M. GORMAN, M.D.
New York, N.Y.

Dr. Laor Replies

SIR: I am sorry that Dr. Gorman is disappointed by my review of Grünbaum's philosophical critique of psychoanalysis. We are only human, however, and cannot claim to understand all, let alone to satisfy all.

Dr. Gorman claims that Grünbaum demonstrates—contrary to Popper—how psychoanalysis is “testable by the standard scientific method.” Furthermore, Dr. Gorman says that I am mistaken in my criticism of Grünbaum's study as hermeneutic: it is irrelevant to his task and might defend an alleged privileged status for the psychoanalyst as scientist of the mind. I have neither understood nor appreciated Grünbaum's study. Are there attenuating circumstances for my grave mistake?

As Dr. Gorman acknowledges, the study is a difficult one to follow due to Grünbaum's heavy literary style and his unnecessarily complex presentation. We learn about his goal and conclusion from the last paragraph of his book: “Popper is quite right that contamination by suggestion does undermine the probative value of clinical data. But . . . insofar as his case against the clinical confirmability of psychoanalysis

is sound, it does not redound to the discredit of inductivism qua method of scientific theory validation” (p. 285).

Whether valid or not, this point is philosophically not a subtle one, and, whatever this point is, it is utterly different from the one ascribed to Grünbaum by Dr. Gorman as quoted above. In fact, it had been already stated, in part, by others before Grünbaum. Suppose it is valid. It is, then, surely devastating. Why write a whole book on a point repeatedly made by others against Popper's theory of science and its application to psychoanalysis? Why write a whole book when the coda of that book can be read and fully understood with almost no reference to the rest of the book? Would Grünbaum have bothered to present us with a laborious study if his argument had been as simple as Dr. Gorman alleges? Would he not qualify the view ascribed to him by Dr. Gorman that “principles and tenets of psychoanalysis are testable by the standard scientific method”?

Grünbaum states his goal quite explicitly: to show that his inductivist—but not Karl Popper's—philosophy “commands the logical resources to derogate the scientific credentials of psychoanalysis” (1). Let the reader compare this quotation from Grünbaum with Dr. Gorman's view of his project as stated above.

As for Grünbaum, he presents us with his hermeneutic of the Freudian corpus, arguing that his philosophical framework of science is the same as Freud's, that it is the only rationally justified one, and that for the most part, psychoanalysis, as it is practiced by hermeneuts and by scientific Freudians, falls outside of it. Whatever this statement may mean, I doubt its usefulness for psychoanalysts. Grünbaum should first tell them what exactly his philosophy of science is.

Grünbaum's challenge is philosophical. It touches on serious matters and, therefore, ought to be met on the same philosophical level at which it was launched. I have attempted to do so in writing (2) as well as in public talks (“We Are Not on Trial,” presented at the meeting of the World Psychiatric Association, Copenhagen, 1986). Grünbaum has chosen not to respond.

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NATHANIEL LAOR, M.D., PH.D.
New Haven, Conn.

Proposed Changes in *DSM-III* Substance Dependence Criteria

SIR: In their article “Proposed Changes in *DSM-III* Substance Use Disorders: Description and Rationale” (April 1986 issue), Bruce J. Rounsaville, M.D., et al. suggested a revised model of dependence based on the idea of impaired control over substance use. There are, however, a number of shortcomings in the proposed changes. The *DSM-III* criteria for alcohol abuse include some symptoms of dependence, e.g., “need for daily use of alcohol.” To solve this contradiction, Dr. Rounsaville and colleagues have removed the abuse category and relocated all, or at least some, abusers into the dependent group. This would artificially increase the

number of dependent alcoholics and eliminate the important difference between abusers and users.

The authors stressed a difficulty with the requirement that social or occupational impairment be shown in order to make the diagnosis of substance use disorders, but by avoiding the problem they throw the baby out with the bath water. A comprehensive classification should include the first-rank clinical criteria and such second-rank criteria as adverse social, occupational, and physical effects.

Dr. Rounsaville and colleagues cite my letter (1), in which I stated that for many older alcoholics, reversed tolerance is displayed, with less substance required to achieve the desired effect. However, in the proposed changes the authors repeat a mistake made in *DSM-III*, contending that tolerance in alcohol dependence is "need for increased amounts of substance in order to achieve intoxication or desired effect, or diminished effect with continued use of same amount" (appendix to their article). They also ignore the fact that increased tolerance may be observed among nondependent users. The authors' critical remarks concerning withdrawal as the index of dependence are not convincing. They claim that diagnostic criteria of withdrawal are unreliable, since they may be equivalent to a hangover "following even a single episode of heavy use" (p. 464 of their article). But in spite of certain phenomenological similarities, there is a principal pathophysiological difference between posttoxic fatigue following a single episode of heavy use of a substance by nonaddictive users, on the one hand, and the withdrawal syndrome associated with physical dependence, on the other.

It is not clear, from the appendix to the article by Dr. Rounsaville and associates, how many items are required to meet a diagnosis of dependence. In the meantime, any estimation of prevalence rates for substance dependence is related to the measurement of items (2). Some criteria suggested by the authors are widely accepted, but the validity of others still needs to be proven.

The authors recommended that physicians determine the severity of dependence by using clinical judgment, but judgmental decisions lead to confusion. Such a proposal also ignores the fact that the stages of dependence differ not only quantitatively but qualitatively, because they represent the phases of the pathological process. The future classification can use a number of the multidimensional models of this process (see, for example, reference 3).

The article is a useful introduction to a discussion on definitions and criteria of substance dependence, but no more than that.

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BORIS M. SEGAL, M.D.
Pleasantville, N.Y.

SIR: The proposal in the article by Dr. Rounsaville and associates to revise the diagnostic classification and criteria

for substance use disorders represents an important conceptual advance, but it is not without problems in its proposed format.

Elimination of the term "abuse" is laudable; it is a vague and value-ridden concept, inconsistently applied. So, to a lesser degree, is "dependence," a word that is undergoing continual conceptual revision. The abuse/dependence dichotomy should be abandoned. However, the continued use of "dependence" invites confusion.

In recent years, "dependence" has gradually taken the place of "addiction," but this terminological change has not wholly succeeded in divesting the label of its pejorative overtones. The proposed revision will increase the proportion of people receiving this deviant label. Furthermore, it will be applied to some who are not "dependent" in the common-sense meaning of the term. Since experts have not yet formed a consensus on the meaning and nature of the phenomenon we call "dependence," it should be avoided. Rather than broaden the definition of an already problematic concept, it would be preferable to employ "use disorder" for all diagnostic categories.

Multiple drug use is so widespread that from an epidemiological viewpoint the "polypsychosubstance dependence" diagnosis in theory would be the most frequently used. Nevertheless, the diagnostician confronted by a patient with conjoint alcohol, tobacco, and benzodiazepine use disorders probably will code only the problems of current clinical relevance. Thus, the "polypsychosubstance" diagnosis in practice will be reserved for the most indiscriminating users, the "garbage heads," as they are called on the street. If there were important treatment implications suggested by a special "garbage head" diagnosis, its reification might be justified; whether the cumbersome terminology used to denote it would also be justified is a moot question. A straightforward "mixed" or "multiple" designation conveys the same information in cases where no particular drug problem predominates.

Furthermore, the desire of the advisory committee to stress that "psychosubstance neuroadaptation syndrome" is an involuntary physiological condition is understandable. However, since the behavioral and cognitive elements usually associated with dependence are absent, would it not be more appropriate to simply note the condition on axis III?

JUDITH BLACKWELL, PH.D.
Toronto, Ont., Canada

SIR: After carefully reading the article by Dr. Rounsaville and colleagues on proposed changes in *DSM-III* substance use disorders, I found that their proposals make more precise and clear the handling of the diagnosis for this type of problem. In the section on polysubstance diagnosis, they suggested that the term "polypsychosubstance dependence" be used, eliminating the category of "mixed substance abuse." It is my feeling that the proposed technical term could be misunderstood, as all the substances are not polypsychosubstance. The term would mean that drugs act in multiple forms, and I am certain that this was not the author's intended meaning.

I suggest that the diagnosis "polypsychosubstance dependence" be eliminated and the diagnosis "psychosubstance polysubstance dependence" be used. This term is more specific for the intended purpose.

ANGEL PRADO, M.D.
Cuernavaca, Mor., Mexico

Dr. Rounsaville and Colleagues Reply

SIR: Since the publication of our article in April 1986, a number of further revisions in the *DSM-III-R* criteria have been made by the Work Group to Revise *DSM-III* in conjunction with the advisory committee on psychoactive substances. These changes, in part, address the concerns expressed in the letters of Drs. Segal, Blackwell, and Prado.

First, and most important, an "abuse" category has been reinstated, with these criteria:

- A. A maladaptive pattern of substance use indicated by at least one of the following:
 - 1) continued use despite a persistent social, occupational, psychological, or physical problem that is caused or exacerbated by use of the substance;
 - 2) recurrent use in situations when use is hazardous (e.g., driving while intoxicated).
- B. Some symptoms of the disturbance have persisted for at least one month, or have occurred repeatedly over a longer period of time.
- C. Never met the criteria for Psychoactive Substance Dependence for this substance.

The principal reason for reintroducing the redefined abuse category was to allow clinicians to determine a diagnosis for individuals whose psychoactive substance use has led to impairment but who have not yet developed a pattern of behaviors indicating sufficient loss of control to qualify them for the diagnosis of dependence. The clinicians most concerned about the need for the newly defined abuse category have been those who work with teen-age and young adult patients, many of whom are referred to treatment because episodic excessive substance use has brought them to the attention of legal or school authorities. Such individuals, while not yet substance dependent, are frequently in need of treatment and may be at an early stage of a disorder that would later meet the criteria for psychoactive substance dependence.

We emphasize that the new abuse category is not equivalent to the *DSM-III* diagnosis. A field trial has demonstrated that nearly all of the individuals whose conditions met *DSM-III* criteria for abuse or dependence met the new and broadened *DSM-III-R* criteria for dependence (1). Hence, the new abuse category is best conceptualized as a residual diagnosis reserved for those with a mild disorder or those who are at an early point in their substance use.

The second major change is the reinstatement of a revised criterion for duration of psychoactive substance dependence or abuse as follows: "Some symptoms of the disturbance have persisted for at least one month, or have occurred repeatedly over a longer period of time." This criterion has been added because field trials have detected individuals whose conditions meet criteria for psychoactive substance use disorders on the basis of only a single, brief episode of heavy use, although clinically the diagnosis did not seem warranted.

We would like to respond now to other points brought up by the correspondence.

1. The diagnostic term for those using multiple psychoactive substances without one predominating has been changed to "polysubstance dependence" (or "abuse"). It is not intended to be used for individuals who meet criteria simultaneously for dependence on each of several different substances. Such individuals should be given multiple diagnoses

(e.g., alcohol dependence and heroin dependence).

2. To clarify a point omitted from our manuscript, "psychoactive substance neuroadaptation syndrome" is not considered a mental disorder and should be noted on axis III.

3. Regarding Dr. Segal's comments on tolerance and withdrawal, we criticized the *exclusive* reliance on these criteria to diagnose dependence but recognize their importance in the overall picture of diminished control over psychoactive substance use. This important but more limited role is denoted by including tolerance and withdrawal as two of nine criteria for dependence. The concept of reversed tolerance was not included in the criteria because it is comparatively rare. In addition, it typically occurs at a late stage of psychoactive substance dependence, so that individuals with this symptom are likely to meet numerous other criteria, thereby preventing a missed diagnosis.

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BRUCE J. ROUNSAVILLE, M.D.
ROBERT L. SPITZER, M.D.
JANET B.W. WILLIAMS, D.S.W.
New Haven, Conn.

Carry-Over Effects of Marijuana

SIR: Proponents of widely applied urine testing for psychoactive drugs frequently cite a paper that was published in the *Journal* (1). In that study, volunteer pilots used a flight simulator that mimics landing an airplane. The apparatus yields a myriad of measures and composite indices, and it reportedly detected impairment 24 hours after the subjects smoked marijuana. The results are surprising, because human impairment more than 4 hours after marijuana use has rarely been described.

We were told little about the subjects, who were recruited by advertisement at a local airport. They were young (their mean age was 29 years) and were experienced users of marijuana, but they were accepted for the study only if they reported smoking it less than daily. They were screened for drug use, although nothing was reported about the method or the results. Ten subjects from an unknown number that were screened were chosen.

The subjects were trained for 8 hours. On the study day they performed on the simulator three times, with the last turn accepted as baseline. They then smoked a marijuana cigarette containing 19 mg of Δ^9 -tetrahydrocannabinol (THC) and were retested 1, 4, and 24 hours later. The 24-hour test was also preceded by two practice runs.

The study was not controlled: "No placebo was used, since prior studies using the same cigarette found that 90% of the subjects could identify the active drug" (p. 1326). Obviously, there was no concealment of active drug from the subjects or experimenters and no control for biasing input from either, nor was there any control for other potential intervening variables such as simulator or computer malfunction or poorly chosen measurements or indices.

The experimenters were concerned about subjects' use of alcohol or marijuana before the 24-hour test. Apparently, they decided to use mild threats: "The subjects were strictly informed (verbally and on the consent forms) that they should not use any alcohol or other drugs of potential abuse

... and that they would in fact be tested for those substances" (pp. 1326, 1328). Despite the threat, the investigators admitted that "there is no way to quantify the results of urine tests (or breath analysis) to rule out such possibilities." No test results were reported.

These poorly characterized subjects carried out the task at least seven times. There was no discussion of the impact of repeated trials nor a discussion of the number of measurements and indices collected. The authors stated that one method of quantifying performance in simulators is to measure everything. When one measures everything, one of 20 measures will yield statistically significant variation.

This was an uncontrolled trial. Even if an active treatment is difficult to blind, that scarcely justifies the lack of controls. Under such circumstances, the authors had no business making only a within-subject comparison and were obligated to assess a parallel group of untreated subjects.

This study contained fatal errors in experimental design. Whatever the authors' intentions, the experiment is now being inappropriately cited to justify employer use of urinary tests for cannabinoids.

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JOHN P. MORGAN, M.D.
New York, N.Y.

Dr. Yesavage Replies

SIR: My colleagues and I have no difficulty in agreeing with Dr. Morgan that the study we submitted was preliminary (it says so in the title). I do find it nonetheless curious how he quotes from the article. For example, we did say point-blank that the subjects were screened by urine test for use of other drugs prior to the study. If our subjects had in fact used THC and their urine samples had remained "dirty" for days after use, we could not have used a urine sample positive for THC on the day of testing as an exclusionary criterion. There is no simple answer to this question, since we cannot use drug-naïve subjects, who are quite likely to overreact to the dose of medication they are given, nor is it really practical to blind subjects to their dose of THC. In current work we are using a placebo (10-mg and 20-mg doses) and the subjects can still tell the placebo from the active drug.

Dr. Morgan also states that we said in the paper that "one method of quantifying performance is to measure everything," implying that this is what we do; in his opinion "one of 20" measures will yield statistically significant variation. He neglects to cite the passage in its entirety: "There are two typical methods of quantifying pilot performance. These are the 'measure everything' approach and the measurement of certain critical points on selected maneuvers. . . . Our approach combined aspects of both." Where he obtains the 20 measures I don't know, since we showed photographs of the computer data output and listed in the table the eight measures we used. The results were rather consistent on these measures.

In any case, we agree that it is unfortunate that some would use this preliminary study as the ultimate word on the subject. On the other hand, I think it is also quite easy to get

carried away in the opposite direction and use rather questionable "proofs" of its lack of merit.

JEROME A. YESAVAGE, M.D.
Stanford, Calif.

Treatment of Anorexia Nervosa

SIR: I would like to thank L.K. George Hsu, M.D., for a comprehensive and well balanced review in "The Treatment of Anorexia Nervosa" (May 1986 issue). However, there were a couple of statements in his article which I think did not accurately reflect our understanding of the disorder or advances in the field.

In particular, in his introduction he stated that "the etiology of the disorder remains unknown." This may be true if one uses the narrow medical model. Indeed, we have not found so far one cause to explain this illness; however, applying the biopsychosocial multidimensional model proposed by Garfinkel and Garner (1) goes a long way in helping us understand the etiology of the disorder. This model emphasizes the biological effects of starvation in perpetuating this disorder, which is precipitated by a stressful event for patients with predisposing individual and family psychological features. In addition, today's North American cultural emphasis on thinness acts as a ubiquitous factor facilitating the occurrence of this illness. The weighing of these factors still needs to be individualized.

Another statement that I question occurred in Dr. Hsu's conclusions. He stated, "Unfortunately, there has been no breakthrough in the treatment of anorexia nervosa in the last 25 years." Indeed, there has not been any major single breakthrough. However, changes in the treatment of anorexia nervosa over the past 25 years have been revolutionary in a quiet and gradual way. As was stated in the article, we have come a long way from the time when individual psychoanalytical approaches were thought to be the treatment of choice. These changes are reviewed by Dr. Hsu: the changes in approach in individual psychotherapy, the emphasis on nutritional rehabilitation, and the use of cognitive behavioral techniques, group therapy, family therapy, and psychoeducational approaches. All this progress may be one of the reasons why the mortality rate for this disorder is no longer as high as it was thought to be 25 years ago (1, pp. 341-342).

In summary, I think we have progressed considerably in furthering our understanding and treatment of this disorder. The prognosis is no longer grim, although the relapse rate remains high. It is my impression that there is progressive improvement in most patients who remain in active treatment programs.

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PIERRE LEICHNER, M.D.
Verdun, Que., Canada

Dr. Hsu Replies

SIR: The points that Dr. Leichner raises touch ultimately on larger questions, such as what models to use in psychiatry

and what "explanation" means in psychiatric research. I shall respond briefly.

1. The etiology of anorexia nervosa remains unknown. It is true that we have advanced to a stage where we can state in general terms that psychiatric illnesses occur as a result of the joint effect of genes and environment (1). For anorexia nervosa, the environmental factors include the current emphasis on slimness in a population that is getting heavier. Other risk factors include being Caucasian, being female, being adolescent, a competitive environment, certain personality characteristics, and a family history of eating disorders, depression, and alcoholism. What we have is a rough model for further research, not a coherent theory of etiology.

2. There has been no breakthrough in the treatment of anorexia nervosa. Thirty years ago psychiatrists such as Dally and Sargent (2) and Stafford-Clark (3) were already using the same principles that I outlined in my article. There certainly has been progress in the sense that our knowledge has become more solid, but there has been no breakthrough. The high relapse rate and uncertain long-term outcome speak to that. True, to treat anorexia nervosa only with psychoanalysis is bad psychiatry, and perhaps more psychiatrists are giving up bad psychiatry, but to consider that as a "breakthrough" is to offer the term a rather unusual and not particularly interesting redefinition.

3. The outcome of anorexia nervosa varies with the duration of follow-up. At 4–8 years after presentation, the mortality is probably less than 5% (4). At 20 years it might be substantially higher (5). Whether there has been a genuine improvement in the mortality rate is debatable; to ascribe the presumed decrease to better treatment is even more so. It may be prudent to attempt to engage a patient and the family by saying that treatment leads to decreased mortality—neither the patient nor the family is likely to ask difficult questions, such as, "Mortality at what point in the follow-up period?" or "How do you know, sir?"—but it certainly would be very unwise if all of us were to assume that the case is closed.

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L.K. GEORGE HSU, M.D.
Pittsburgh, Pa.

Tardive Dyskinesia: A Serious Side Effect?

SIR: The American Psychiatric Association (APA) and its representatives should stop being so wishy-washy about tardive dyskinesia. In July 1985 APA mailed a two-page letter to members describing 1) its growing concern about tardive dyskinesia, 2) a major educational campaign aimed at professionals and the public, and 3) the establishment of a second task force on tardive dyskinesia. The APA letter

followed on the heels of an announcement by the Food and Drug Administration that it would require a lengthy class warning with all neuroleptics. Both of these developments were featured in the *Psychiatric News* of May 17, 1985, which also ran a story on a 2-million dollar award to a victim of tardive dyskinesia.

Only 1 year later, the *Journal* published an editorial, "Regulation of Psychiatric Practice," by Ross J. Baldessarini, M.D., and Bruce M. Cohen, M.D., (June 1986 issue) stating that "tardive dyskinesia is rarely, if ever, life-threatening. In fact, the putative menace of tardive dyskinesia has, to some extent, been exaggerated. Only a small proportion of patients treated with neuroleptics suffer disabling or irreversible dyskinesia." Well! Why all the fuss? The authors wondered, too, noting "recent alarmist views" regarding tardive dyskinesia and how such views (not described) have led to the notion of requiring written informed consent. The authors claim that this would be an "unprecedented intrusion" into a treatment "acknowledged as acceptably safe and effective."

Acceptably safe for whom? Indeed, safety remains a significant issue (as does the risk-benefit ratio, but that cannot be discussed here). The 1980 Task Force on Tardive Dyskinesia (chaired by Dr. Baldessarini) found that tardive dyskinesia may be permanent in up to 50% of chronic patients ("a conservative estimate") (1). Further, "patients with severe dystonias can be severely disabled." Dr. Baldessarini added in a 1985 article (2) that tardive dyskinesia "can be embarrassing and distressing. . . . In some cases, self-care, feeding and swallowing, as well as vocationally important dexterity, can be impaired; severe cases, while infrequent, can be as disabling as Huntington's disease." Lazarus and Toglia (3) described the fatal outcome of myoglobinuric renal failure in a 45-year-old woman with severe tardive dyskinesia, stressing that "the potential for serious motor disability is generally underestimated" and noting that persistent retching, vomiting, weight loss, and dehydration can occur, with respiratory or gastrointestinal involvement. Given the difficulties of predicting the risk or course of complications in the individual patient, these descriptions should be alarming, not alarmist.

The authors' claim that irreversible dyskinesia occurs in only a small proportion of patients not only runs counter to the findings of the 1980 task force but also to those in the review of Jeste and Wyatt (4), who found that 36.5% of patients withdrawn from neuroleptics had a remission. It is worth recalling that remission usually means a 50% reduction in the patient's score on the Abnormal Involuntary Movement Scale (5); clearly, important symptoms may remain.

One hopes that education will make regulation less attractive, but it is difficult to see how an editorial "band-aid" over our Achilles' heel enhances knowledge. Written informed consent, even with all its problems (and whether required or not), might well be helpful in sharpening the educational focus on this deeply troubling iatrogenic disorder.

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CHARLES E. DEAN, M.D.
Minneapolis, Minn.

Drs. Baldessarini and Cohen Reply

SIR: Dr. Dean's letter raises several points that deserve comment. First, we presented our own opinions in our editorial and do not speak for APA. In our view, APA has acted appropriately by consistently seeking to gather and present the available facts concerning the important problem of tardive dyskinesia. Also, we agree that it is reasonable and helpful for the U.S. Food and Drug Administration to require clear information in product inserts concerning the side-effect risks for neuroleptic as well as other agents. We are aware that tardive dyskinesia, in particular, has been a subject of litigation in malpractice suits involving psychiatrists, and we believe that it is an issue of serious concern. The facts about tardive dyskinesia and other side effects clearly require prudent physicians to use neuroleptic and other psychotropic agents thoughtfully and wisely, as stated in our editorial.

Since the publication by APA in 1980 of the first comprehensive report on tardive dyskinesia, cited by Dr. Dean, there has been a considerable advance in knowledge about the condition. Recent studies and experience do not support the older view that most cases of tardive dyskinesia are severe and irreversible. The best estimate of the prevalence of clinically significant tardive dyskinesia, corrected for spontaneous and idiopathic dyskinesias, is about 15%-20% in patients treated for more than 6 months, with an annual incidence of about 2%-5% for the first 0.5-4 years (1). With prolonged follow-up, sometimes for several years, the majority of patients show gradual improvement or eventual remission, particularly if neuroleptic medication is stopped or the dose lowered (1).

Only a minority of patients treated with neuroleptic agents develop irreversible tardive dyskinesia, and very few suffer severe incapacitation. Moreover, and also as noted in our editorial, there is a relatively new but growing body of data which suggests that the risk of tardive dyskinesia may be limited further by the use of minimum effective doses of neuroleptic agents (1-3). Finally, it is important to note for the sake of clarity that the cases of life-threatening reactions to neuroleptic agents described in Dr. Dean's letter do not necessarily represent straightforward examples of tardive dyskinesia. Fatalities can occur in acute neuroleptic dystonia and in the neuroleptic malignant syndrome, with which tardive dyskinesia may coexist or be confused (2).

Our conclusions are not meant to trivialize the problems associated with the use of neuroleptics. Rather, we think they are reasonable views that incorporate current knowledge about these problems. Again, we do not say that neuroleptics are agents without serious risks but, instead, contend that these iatrogenic risks need to be balanced against the medical risks associated with the psychoses themselves, which can include fatal outcomes (4). Balancing benefits and risks in this situation remains a matter of informed clinical judgment, as in the treatment of any medical disorder. All drug treatments (e.g., penicillin for pneumonia or quinidine for

cardiac arrhythmia) have attendant, sometimes life-threatening, risks, but written consent forms are not used for them. The tone of Dr. Dean's comments suggest that neuroleptic agents should be discarded as not acceptably safe in proportion to their benefits. In agreement with the Food and Drug Administration, we find that the evidence contradicts this position. Nonetheless, we strongly support the search for safer and more effective treatments for psychotic patients.

Finally, we and others (5) have suggested that obtaining written informed consent (evidently supported by Dr. Dean) is a poor means of ensuring transmittal of information or of minimizing the risk of accusation of malpractice in the use of neuroleptic agents. We suspect that the use of such mechanisms is an excellent example of a "band-aid," to borrow his term, and may well distract us from the more important issues of educating and monitoring ourselves and our patients.

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ROSS J. BALDESSARINI, M.D.
BRUCE M. COHEN, M.D., PH.D.
Belmont, Mass.

Keeping the Clinician-Researcher Alive

SIR: I was delighted to read "The Clinician-Researcher in Psychiatry" by Jack D. Burke, Jr., M.D., et al. (August 1986 issue). This article pointed out dramatically the growing need for more academic psychiatrists to obtain research training. Burke and his colleagues outlined how this goal can be accomplished during residency training for trainees who lack research skills upon completion of medical school. However, the authors failed to address the rare yet existing problem of those individuals who enter residency already proficient in research skills, having previously earned a Doctor of Philosophy or Master's degree in a basic science discipline, i.e., the medical scientists. These individuals should not be isolated from research for 4 years while "paying their dues" in a standard residency program. The loss to our profession and society is enormous, as the medical scientist is the most prepared to become the clinician-researcher. Specialized training tracks must be designed for such individuals. Chairmen should examine their training programs in order to implement modifications oriented toward training the clinician-researcher. The goals of such changes should be not only to foster growth in research skills among all academically oriented residents but also to design specialized training tracks for residents who already possess well developed research skills. Integration of clinical work with research should be a constant theme. Only by exercising such flexi-

bility can we truly develop and maintain the clinician-researcher.

MARTHA M. SARASUA, M.D., PH.D.
Charleston, S.C.

Dr. Burke and Colleagues Reply

SIR: We agree that academic leaders must be sensitive to the interests, experience, and background of their trainees, including those already trained in a basic science discipline. Providing integrated research and clinical training opportunities for residents with prior research training will be increasingly important as psychiatry attracts more graduates from M.D.-Ph.D. programs.

One caution we should raise in responding to Dr. Sarasua, though, is our view that clinician-researchers need to develop a core identity as *clinicians*, with comfort and competence in that role. The essential goal of basic clinical training needs to be kept in focus for all trainees, including those with prior credentials in a research field.

JACK D. BURKE, JR., M.D., M.P.H.
HAROLD ALAN PINCUS, M.D.
HERBERT PARDES, M.D.
Rockville, Md.

Serotonin Reuptake Inhibitors and DST Status

SIR: While the dispute on the ultimate clinical usefulness of the dexamethasone suppression test (DST) goes on, Walter Armin Brown, M.D., and his colleagues, in "Pituitary-Adrenocortical Hyperfunction and Intolerance to Fluvoxamine, a Selective Serotonin Uptake Inhibitor" (January 1986 issue), introduced another interesting application of the test. They noted that nonsuppression on the DST predicted a high likelihood of nausea and vomiting among patients who received fluvoxamine, a new serotonin-uptake-inhibiting antidepressant. This intriguing finding was interpreted as an indication of enhanced serotonin activity, since compelling evidence suggests that central serotonin activates pituitary-adrenal circuits, identified by nonsuppression of cortisol on the DST.

We completed a protocol designed to evaluate the antidepressant effect of fluoxetine, which is another selective serotonin inhibitor (1). As part of the study we gave a DST to 12 drug-free patients 2 days before fluoxetine administration. The DST was carried out in the standard way (2) after confounding factors such as medical illness, weight loss, acute admission stress, and drug withdrawal had been carefully excluded. We analyzed cortisol by radioimmunoassay and found in eight patients post-DST plasma cortisol concentrations above 5 µg/dl, which we defined as nonsuppression according to our normative data base. Only one patient, who was a nonsuppressor, experienced transient nausea during fluoxetine treatment, while the other seven nonsuppressors and the four suppressors showed no adverse effects, including vomiting. This absence of an association between abnormal DST status and intolerance of fluoxetine suggests to us that it is premature for Dr. Brown and colleagues to conclude that nonsuppression on the DST predicts, in general, adverse response to serotonin-uptake-inhibiting drugs.

One problem arises from the hypothesis that nonsuppres-

sion of cortisol on the DST stems from a serotonin-driven enhancement of the hypothalamic-pituitary-adrenocortical (HPA) axis. In vitro studies have shown that serotonin exerts a stimulating effect on the corticotropin-releasing-hormone (CRH)-secreting neurons (3). However, recent results in normal control subjects illustrated that even a supraphysiologic dose of exogenously administered CRH fails to induce escape from suppression on the DST (4), which renders identification of CRH hyperactivity with nonsuppression of cortisol on the DST doubtful. Therefore, other factors that are not necessarily regulated by central serotonin are apparently essential corequirements for inducing nonsuppression on the DST. Another problem in the interpretation of data by Dr. Brown and his associates is the results of Kletzky et al. (5), who showed the absence of any endocrine effect of fluvoxamine on the HPA axis.

Given these considerations, we suspect that some other mechanisms besides serotonin uptake inhibition must be taken into account to explain the potentially interesting association of untoward side effects of fluvoxamine and nonsuppression on the DST.

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FLORIAN HOLLSBOER, M.D., PH.D.
ULRICH VON BARDELEBEN, M.D.
Mainz, Federal Republic of Germany

Dr. Brown and Associates Reply

SIR: We, too, looked at the DST and response to fluoxetine and included our results in a presentation at the 1985 World Congress of Biological Psychiatry (1). Like Drs. Holsboer and von Bardeleben, we found that among depressed patients treated with 20-60 mg/day of fluoxetine, two of 15 nonsuppressors and none of 20 suppressors reported nausea. Not surprisingly, the rate of all side effects was dose dependent, appearing in 31%, 44%, and 56% of patients treated with 20, 40, and 60 mg, respectively. Among the patients taking 60 mg of fluoxetine, five of nine suppressors and three of four nonsuppressors discontinued the drug because of side effects; no suppressors, but one nonsuppressor, discontinued because of nausea. We wonder whether the low rate of nausea with fluoxetine compared to the rate we observed with fluvoxamine might be accounted for by differences in dose. The low rate of adverse effects in fluoxetine-treated patients that both we and Drs. Holsboer and von Bardeleben found obscures any relationship that might exist between such effects and nonsuppression on the DST. Nonetheless, it

has not escaped our attention that the few patients who experienced nausea when taking fluoxetine were nonsuppressors.

Drs. Holsboer and von Bardeleben take issue with our *speculation*, derived from serotonin's recognized stimulatory effect on the pituitary-adrenocortical axis, that nonsuppression on the DST in depressed patients is related to a functional increase in central serotonin activity. They seem to argue that, since serotonin stimulates CRH release and since they found that administration of CRH does not induce escape from suppression on the DST, other factors "not necessarily regulated by central serotonin" are required to induce nonsuppression. Even if this were so, it would not alter the validity of the hypothesis that nonsuppression on the DST associated with depression is related to a functional increase in central serotonin activity; this "serotonin" hypothesis does not imply involvement of CRH or exclusion of other neurotransmitters and neurohormones. Furthermore, Drs. Holsboer and von Bardeleben, in their own cited work (their reference 4), show that administration of CRH to dexamethasone-treated healthy people induces a clear increase in plasma cortisol, not seen with placebo or lysine vasopressin, to a mean peak of 4.1 $\mu\text{g/dl}$. Since this plasma cortisol concentration lies below 5.0 $\mu\text{g/dl}$, a common criterion for nonsuppression on the DST, they concluded—perhaps correctly, perhaps not—that CRH itself does not induce escape from dexamethasone suppression. The results of their notably elegant study are subject to several interpretations; one is that CRH, which is stimulated by serotonin, is likely to participate in the phenomenon of nonsuppression.

As for the study by Kletzky et al. (reference 5 in Dr. Holsboer and Dr. von Bardeleben's letter), which apparently showed "the absence of any endocrine effect of fluvoxamine upon the HPA axis" in healthy men, we had not been aware of this paper and read it with great interest. The authors' conclusions, accurately reported by Drs. Holsboer and von Bardeleben, were puzzling in light of the regularity with which other serotonin agonists stimulate the pituitary-adrenocortical system and the clear stimulating effect of fluvoxamine on β -endorphin and β -lipotropin in rats (2). Upon inspection of the data of Kletzky et al. (p. 397), we discovered that whereas fluvoxamine, 50 mg every 8 hours for 24 hours, did not affect the cortisol response to hypoglycemia or average plasma cortisol concentrations, both plasma cortisol and prolactin appeared to increase within 3 hours after fluvoxamine administration.

Having said all this, we would like to emphasize, in agreement with Drs. Holsboer and von Bardeleben, that we do not have a clear, let alone airtight, explanation for the association we observed between fluvoxamine's side effects and pituitary-adrenocortical function.

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WALTER A. BROWN, M.D.
MIHALY ARATO, M.D., PH.D.
RAM SHRIVASTAVA, M.D.
Providence, R.I.

Lithium and Extrapyramidal Side Effects of Neuroleptics

SIR: In "Safety of the Combination of Lithium and Neuroleptic Drugs" by Robert D. Goldney, M.D., and Neil D. Spence, Ph.D., (July 1986 issue), the authors conclude that lithium does not increase morbidity from the extrapyramidal side effects of neuroleptics. Unfortunately, this conclusion is unwarranted on the basis of their data because of the following serious methodologic problems.

First, there is no mention of either the type or the relative severity of the diagnosed extrapyramidal side effects despite the fact that these effects range from clinically insignificant to life threatening. Second, the side effects were only followed for a mean of 4 days—hardly enough time, since severe extrapyramidal side effects often take much longer to develop (1). Only longer follow-up, in which morbidity in the groups of subjects is evaluated later during hospitalization, would be clinically meaningful. Third, a chart review as a means of diagnosing extrapyramidal side effects is inadequate. Clinicians who care for acutely psychotic patients frequently do not make a diagnosis (2), and consequently these side effects will not be documented in the clinical record. From my clinical experience and the general literature on extrapyramidal side effects, it is difficult to accept a total prevalence rate of only 26% when the mean neuroleptic dosage was over 3,000 mg of chlorpromazine equivalents. This suggests that there was considerable underrecognition of these side effects.

My major point is that the authors seem to have missed several important factors when they initially designed their study. The natural history, differential clinical consequences, and subtypes of extrapyramidal side effects, as well as the severe limitations inherent in the accuracy of a chart review for ascertaining these side effects, were not considered. I urge that future reports which evaluate such complications take more seriously these methodologic issues in order to make the data clinically relevant.

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PETER WEIDEN, M.D.
New York, N.Y.

Drs. Goldney and Spence Reply

SIR: We agree with Dr. Weiden that there are shortcomings in the delineation of extrapyramidal side effects and acknowledged this in our paper. The study was a retrospective analysis of records rather than a planned research project, and the subjects were unusual in the sense that they were the most severely psychotic seen in psychiatric practice, with the majority having been compulsorily hospitalized. Such patients are not usually the subjects of research reports, and this is no doubt the main reason for the high doses of drugs that were noted. It has been reported that high doses of neuroleptics "may actually decrease both the incidence and severity of EPS" (1), and so there may not be as much underrecognition of these side effects as Dr. Weiden suggests.

Norwithstanding these shortcomings, there is no reason to

suspect that extrapyramidal side effects would be reported more or less for either of the groups studied; therefore we believe that the finding that the combination of lithium and neuroleptics was not more likely to produce such side effects than neuroleptics alone still holds.

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ROBERT D. GOLDNEY, M.D.
NEIL D. SPENCE, PH.D.
Adelaide, Australia

Cerebral Ischemic Symptoms in Anxiety Disorders

SIR: Patricia K. Coyle, M.D., and Arnold B. Sterman, M.D., reported in "Focal Neurologic Symptoms in Panic Attacks" (May 1986 issue) that panic attacks manifested as focal neurological symptoms in 5% of the referrals to a neurology service. We studied the prevalence of symptoms suggestive of cerebral ischemia in 16 patients who met the DSM-III criteria for agoraphobia with panic, 26 patients with generalized anxiety disorder, and normal volunteers of comparable age and sex distribution. In both the patient group and the control group there were 19 men and 23 women; the mean \pm SD age of the male patients was 43 ± 15.2 years; of the male control subjects, 44.7 ± 15.1 ; of the female patients, 42.8 ± 15.0 ; and of the female control subjects, 39.4 ± 15.9 . Both the patients and the control subjects were physically healthy and free of all medication for 2 weeks before the study. Anxiety was quantified by using the State-Trait Anxiety Inventory (1) and depression by using the Beck Depression Inventory (2). Cerebral ischemic events were evaluated by means of a questionnaire, developed for use in a neurology clinic to identify patients with transient ischemic attacks (TIAs), which provided information on the frequency, duration, and nature of such common symptoms of TIAs as loss of speech and vision, tingling and numbness, weakness and paralysis, and dizziness and fainting. Symptoms induced by postural changes, head movements, and keeping limbs in a fixed position for long periods of time were not counted as ischemic symptoms.

When the two groups were compared by analysis of variance, the patients had a significantly ($p < .001$) higher prevalence of all cerebral ischemic symptoms except loss of vision (dizziness, 47%; tingling, 37%; loss of speech, 32%; weakness and paralysis, 16%). There were no differences between patients who had agoraphobia and patients who had generalized anxiety disorder. Multiple regression analysis, with the ischemic symptoms (total) as the criterion variable and depression, state anxiety, and trait anxiety scores as predictor variables, identified state anxiety as the factor that explained the largest percentage of variance (semipartial $r^2 = .239$; partial $r^2 = .339$).

Symptoms reported by the patients differed from classic TIAs in several ways. TIAs, by definition, last from 5 to 15 minutes, whereas the anxious patients' symptoms usually lasted less than 2 minutes. Unlike TIAs, these symptoms were unrelated to age, and even patients who gave a long history (more than 10 years) of such symptoms did not have any demonstrable neurological deficits. TIA patients often suffer

from a variety of physical disorders, unlike these anxious patients, who were physically healthy. Forty-seven percent of the patients reported dizziness, and three subjects had fainting spells. Dizziness and fainting in the absence of other symptoms are not indicative of focal ischemia and are not accepted as typical transient ischemic symptoms. These are probably caused by a sudden drop in perfusion pressure. In the anxiety patients, these symptoms were precipitated by acute elevations in state anxiety.

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ROY J. MATHEW, M.D.
WILLIAM H. WILSON, PH.D.
PERRY M. NICASSIO, PH.D.
Durham, N.C.

Drs. Coyle and Sterman Reply

SIR: We were very interested in the study by Drs. Mathew, Wilson, and Nicassio, which takes an approach different from ours but makes similar observations. They screened a psychiatric population for neurologic complaints that are generally considered ischemic. Although detailed symptom descriptions are not provided, Dr. Mathew and colleagues describe a high prevalence of TIA-like complaints, including speech loss, tingling, and weakness and paralysis—findings similar to our data. Also similar to our observations, they describe a long history of symptoms occurring in relatively young and healthy patients, who had normal findings on neurologic examination. These clinical observations raise interesting experimental questions with regard to the mechanisms of anxiety-induced neurologic symptoms. We thank Dr. Mathew and associates for sharing their study with us and hope our clinical reports will give further input to those who are working in the area of brain-behavior interactions and studying the precise mechanisms that relate acute elevations in anxiety state to the appearance of symptoms and signs of neurologic and cardiovascular dysfunction.

PATRICIA K. COYLE, M.D.
Stony Brook, N.Y.
ARNOLD B. STERMAN, M.D.
East Hanover, N.J.

Carbamazepine, Alprazolam Withdrawal, and Panic Disorder

SIR: In "Preliminary Evidence for the Utility of Carbamazepine in Alprazolam Withdrawal" (February 1986 issue), Ehud Klein, M.D., and colleagues suggested that carbamazepine may be useful in the treatment of benzodiazepine withdrawal. They describe three patients with panic disorder who developed "withdrawal symptoms" when alprazolam dosage was reduced and then experienced remission of "withdrawal symptoms" with the addition of carbamazepine. We do not know whether these patients continued to take carbamazepine after successful withdrawal of alprazolam or what became of the original panic symptoms.

While the authors admit that it can be difficult to differentiate withdrawal symptoms from reemergent panic symp-

toms, they do not consider that carbamazepine may have inherent antipanic properties and may act to suppress reemergent panic symptoms rather than alleviate the symptoms of alprazolam withdrawal. Tricyclic antidepressants, notably imipramine, have antipanic activity (1). The antidepressant effect of carbamazepine (2) may be related to its tricyclic nucleus, and this same structural feature could, theoretically, confer antipanic activity on this drug.

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BRIAN A. LAWLOR, M.D.
Gainesville, Fla.

Dr. Klein and Associates Reply

SIR: Dr. Lawlor raises two questions regarding the use of carbamazepine in the treatment of three panic disorder patients undergoing alprazolam withdrawal: 1) Did the patients continue to take carbamazepine, and what was the subsequent course? 2) Could carbamazepine "act to suppress reemergent panic symptoms rather than alleviate the symptoms of alprazolam withdrawal"?

In fact, both of these issues were addressed in the original article. First, we noted that for two patients (cases 1 and 3), carbamazepine was continued as a single drug but was much less effective than alprazolam. Patient 2 subsequently had a carbamazepine trial that was clinically ineffective in the management of her panic disorder.

Second, we stated that "one could argue that this [carbamazepine's apparent efficacy] is not an antiwithdrawal effect but simply the replacement of one anxiolytic drug with another." While there are important differences in the underlying mechanisms of action between carbamazepine and imipramine (1), this statement was included because, as noted by Dr. Lawlor, carbamazepine does have a chemical structure similar to that of imipramine, an agent unequivocally effective in the treatment of panic disorder. In addition to this structural similarity, carbamazepine is very effective in inhibiting limbic seizures induced by a variety of stimuli (2). Since limbic system dysfunction has been postulated in the pathogenesis of panic disorder, one might argue from this perspective as well that carbamazepine's efficacy in the three alprazolam-withdrawal cases was related to an antipanic mechanism of action.

Unfortunately, our experience to date with carbamazepine in the treatment of 10 panic disorder patients has been relatively unimpressive, including the three patients in the report under discussion. While carbamazepine does appear

to have mild to moderate antianxiety properties in some patients (3, 4), carbamazepine's most noteworthy effects in panic patients in our clinic have been the reduction of help-seeking behavior and dysphoria rather than blockade of panic attacks. Of interest, we found carbamazepine effective as an antipanic agent in the treatment of a patient with cocaine-induced panic attacks who later developed spontaneous panic attacks unrelated to cocaine use (5).

As we noted in the original article, carbamazepine itself does not act at the central benzodiazepine receptor site and is not associated with tolerance or withdrawal effects. Thus, the apparent effects of carbamazepine on alprazolam withdrawal cannot be attributed to the substitution of one benzodiazepine compound for another benzodiazepine-like compound.

It should be underscored that carbamazepine's effects on alprazolam withdrawal were reported for only three patients. In a fourth case studied subsequently, we did not find carbamazepine effective in the treatment of alprazolam withdrawal, although this fourth patient had carbamazepine blood levels of only 5 µg/ml, which is at or below the range (6-12 µg/ml) generally used in the successful treatment of complex partial seizures and bipolar illness. Thus, our comments regarding carbamazepine's effects in the treatment of both alprazolam withdrawal and panic disorder are preliminary and require confirmation with double-blind, controlled trials for a larger sample of patients.

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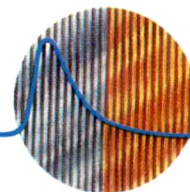
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EHUD KLEIN, M.D.
THOMAS W. UHDE, M.D.
ROBERT M. POST, M.D.
Bethesda, Md.

Reprints of Letters to the Editor are not available.

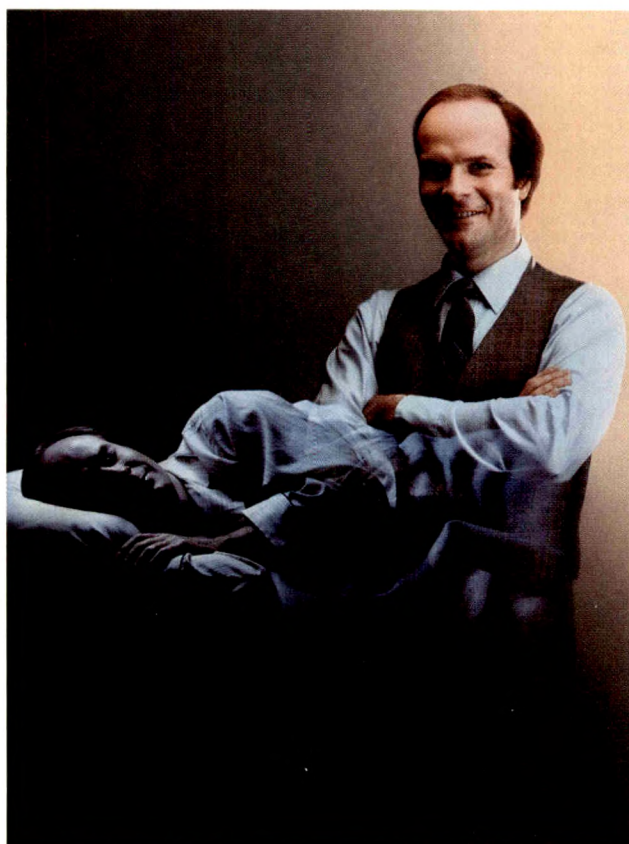
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triazolam 



Helps Meet Both Goals Of Insomnia Therapy

**Improved
Sleep**



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Alertness**

- *Rapidly Absorbed*
- *Promptly Excreted*

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Kalamazoo, Michigan 49001 USA

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Please see adjacent page for brief summary of prescribing information.

Halcion® Tablets (triazolam)

INDICATIONS AND USAGE: HALCION Tablets are indicated in the short-term management of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings, and/or early morning awakenings.

It is recommended that HALCION not be prescribed in quantities exceeding a one-month supply.

CONTRAINDICATIONS: Patients with known hypersensitivity to this drug or other benzodiazepines.

HALCION is contraindicated in pregnant women due to potential fetal damage. Patients likely to become pregnant while receiving HALCION should be warned of the potential risk to the fetus.

WARNINGS: Overdosage may occur at four times the maximum recommended therapeutic dose. Patients should be cautioned not to exceed prescribed dosage.

Because of its depressant CNS effects, patients should be cautioned against engaging in hazardous occupations requiring complete mental alertness and also about the simultaneous ingestion of alcohol and other CNS depressant drugs.

Anterograde amnesia and paradoxical reactions have been reported with HALCION and some other benzodiazepines.

PRECAUTIONS: *General:* In elderly and/or debilitated patients, treatment should be initiated at 0.125 mg to decrease the possibility of development of oversedation, dizziness, or impaired coordination. Caution should be exercised in patients with signs or symptoms of depression which could be intensified by hypnotic drugs. Suicidal tendencies and intentional overdosage is more common in these patients. The usual precautions should be observed in patients with impaired renal or hepatic function and chronic pulmonary insufficiency. *Information for Patients:* Alert patients about: (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing prescribed dosage, (e) possible worsening of sleep after discontinuing HALCION. *Laboratory Tests:* Not ordinarily required in otherwise healthy patients. *Drug Interactions:* Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistaminics, ethanol, and other CNS depressants. Pharmacokinetic interactions of benzodiazepines with other drugs have been reported, e.g., coadministration with either cimetidine or erythromycin reduced clearance, prolonged elimination half-life, and approximately doubled plasma levels of triazolam, hence increased clinical observation and consideration of dosage reduction may be appropriate. *Carcinogenesis, Mutagenesis, Impairment of Fertility:* No evidence of carcinogenic potential was observed in mice during a 24-month study with HALCION in doses up to 4000 times the human dose. *Pregnancy:* Benzodiazepines may cause fetal damage if administered during pregnancy. The child born of a mother who is on benzodiazepines may be at some risk for withdrawal symptoms and neonatal flaccidity during the postnatal period. *Nursing Mothers:* Administration to nursing mothers is not recommended. *Pediatric Use:* Safety and efficacy in children below the age of 18 have not been established.

ADVERSE REACTIONS: During placebo-controlled clinical studies in which 1003 patients received HALCION Tablets, the most troublesome side effects were extensions of the pharmacologic activity of HALCION, e.g., drowsiness, dizziness, or lightheadedness.

	HALCION	Placebo
Number of Patients	1003	997
% of Patients Reporting:		
Central Nervous System		
Drowsiness	14.0	6.4
Headache	9.7	8.4
Dizziness	7.8	3.1
Nervousness	5.2	4.5
Lightheadedness	4.9	0.9
Coordination Disorder/Ataxia	4.6	0.8
Gastrointestinal		
Nausea/Vomiting	4.6	3.7

In addition, the following adverse events have been reported less frequently (i.e., 0.9-0.5%): euphoria, tachycardia, tiredness, confusional states/memory impairment, cramps/pain, depression, visual disturbances.

Rare (i.e., less than 0.5%) adverse reactions included constipation, taste alterations, diarrhea, dry mouth, dermatitis/allergy, dreaming/nightmares, insomnia, paresthesia, tinnitus, dysesthesia, weakness, congestion, death from hepatic failure in a patient also receiving diuretic drugs.

The following adverse events have been reported in association with the use of benzodiazepines: dystonia, irritability, anorexia, fatigue, sedation, slurred speech, jaundice, pruritus, dysarthria, changes in libido, menstrual irregularities, incontinence and urinary retention.

As with all benzodiazepines, paradoxical reactions such as stimulation, agitation, increased muscle spasticity, sleep disturbances, hallucinations and other adverse behavioral effects may occur rarely and in a random fashion. Should these occur, use of the drug should be discontinued.

No laboratory changes were considered to be of physiological significance.

When treatment is protracted, periodic blood counts, urinalysis and blood chemistry analyses are advisable.

Minor changes in EEG patterns, usually low-voltage fast activity have been observed in patients during HALCION therapy and are of no known significance.

DRUG ABUSE AND DEPENDENCE: *Controlled Substance:* HALCION Tablets are a Controlled Substance in Schedule IV. *Abuse and Dependence:* Withdrawal symptoms have occurred following abrupt discontinuance of benzodiazepines. Patients with a history of seizures are at particular risk. Addiction-prone patients should be closely monitored. Repeat prescriptions should be limited to those under medical supervision.

OVERDOSAGE: Because of the potency of triazolam, overdosage may occur at 2 mg, four times the maximum recommended therapeutic dose (0.5 mg). Manifestations of overdosage include somnolence, confusion, impaired coordination, slurred speech, and ultimately, coma. Respiration, pulse, and blood pressure should be monitored and supported by general measure when necessary. Immediate gastric lavage should be performed. Multiple agents may have been ingested.

Store at controlled room temperature 15°-30°C (59°-86°F).

Caution: Federal law prohibits dispensing without prescription.

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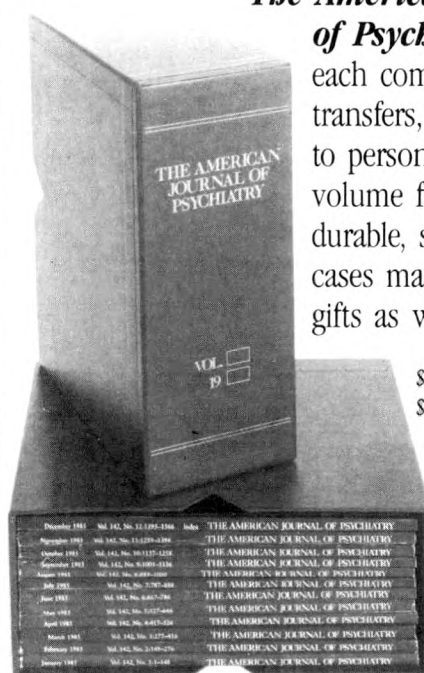
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Talley, Executive Secretary, Charles B. Slack, Inc., 6900 Grove Rd., Thorofare, NJ 08086; 609-848-1000.

May 6-10, annual meeting, American Psychoanalytic Association, Chicago. Contact Helen Fischer, Administrative Director, 309 East 49th St., New York, NY 10017; 212-752-0450.

May 6-10, annual meeting, Society of Biological Psychiatry, Chicago. Contact Philip A. Berger, M.D., Secretary-Treasurer, Dept. of Psychiatry, Stanford University School of Medicine, Stanford, CA 94305; 415-723-0852.

May 7-10, annual meeting, American Academy of Psychoanalysis, Chicago. Contact Vivian Mendelsohn, Executive Director, 30 East 40th St., Suite 608, New York, NY 10016; 212-679-4105.

May 8-10, annual meeting, American Society for Adolescent Psychiatry, Chicago. Contact Mary D. Staples, Executive Director, 24 Green Valley Rd., Wallingford, PA 19086; 215-566-1054.

May 9, annual meeting, American College of Psychoanalysts, Chicago. Contact Leo Madow, M.D., Secretary General, Institute of Pennsylvania Hospital, 111 North 49th St., Philadelphia, PA 19139; 215-471-2339.

May 9, annual meeting, American Society of Psychoanalytic Physicians, Chicago. Contact Mrs. Deborah C. Skolnik, Executive Director, 904 Dryden St., Silver Spring, MD 20901; 301-681-7385.

May 9-15, annual meeting, American Psychiatric Association, Chicago. Contact Cathy Earnest, APA, 1400 K St., N.W., Washington, DC 20005; 202-682-6237.

May 9-15, annual meeting, Christian Medical Society, Psychiatry Section, Chicago. Contact R. Bronson Stilwell, M.D., President, 4171 Crossover Rd., "E", Fayetteville, AR 72701; 501-521-5076.

May 10, annual meeting, American Association of Community Mental Health Center Psychiatrists, Chicago. Contact Gordon H. Clark, Jr., M.D., President, 88 Gale Ave., Laconia, NH 03246; 603-524-1255.

May 11, Diagnosis and Treatment of Depression: Quo Vadis? Sanofi Recherche, Montpellier, France. Contact Scientific Secretariat, Dr. Perla Roset-Danan, Centre de Recherches CLIN-MIDY/SANOFI, Rue du Pr. J. Blayac, 34082 Montpellier Cedex, France; 67-40-01-33; Telex 480 240.

May 11-15, annual meeting, Royal Australian and New Zealand College of Psychiatrists, Auckland, New Zealand. Contact Administrative Secretary, 101 Rathdowne St., Carlton 3053, Victoria, Australia; 03-663-5466.

May 14-17, annual meeting, American Geriatrics Society, New Orleans. Contact Linda Hiddeman Barondess, Executive Vice-President, 10 Columbus Circle, Suite 1470, New York, NY 10019; 212-582-1333.

May 16, annual meeting, Recovery, Incorporated (Association of Nervous and Former Mental Patients), Chicago. Contact Robert L. Farwell, Executive Director, 802 North Dearborn St., Chicago, IL 60610; 312-337-5661.

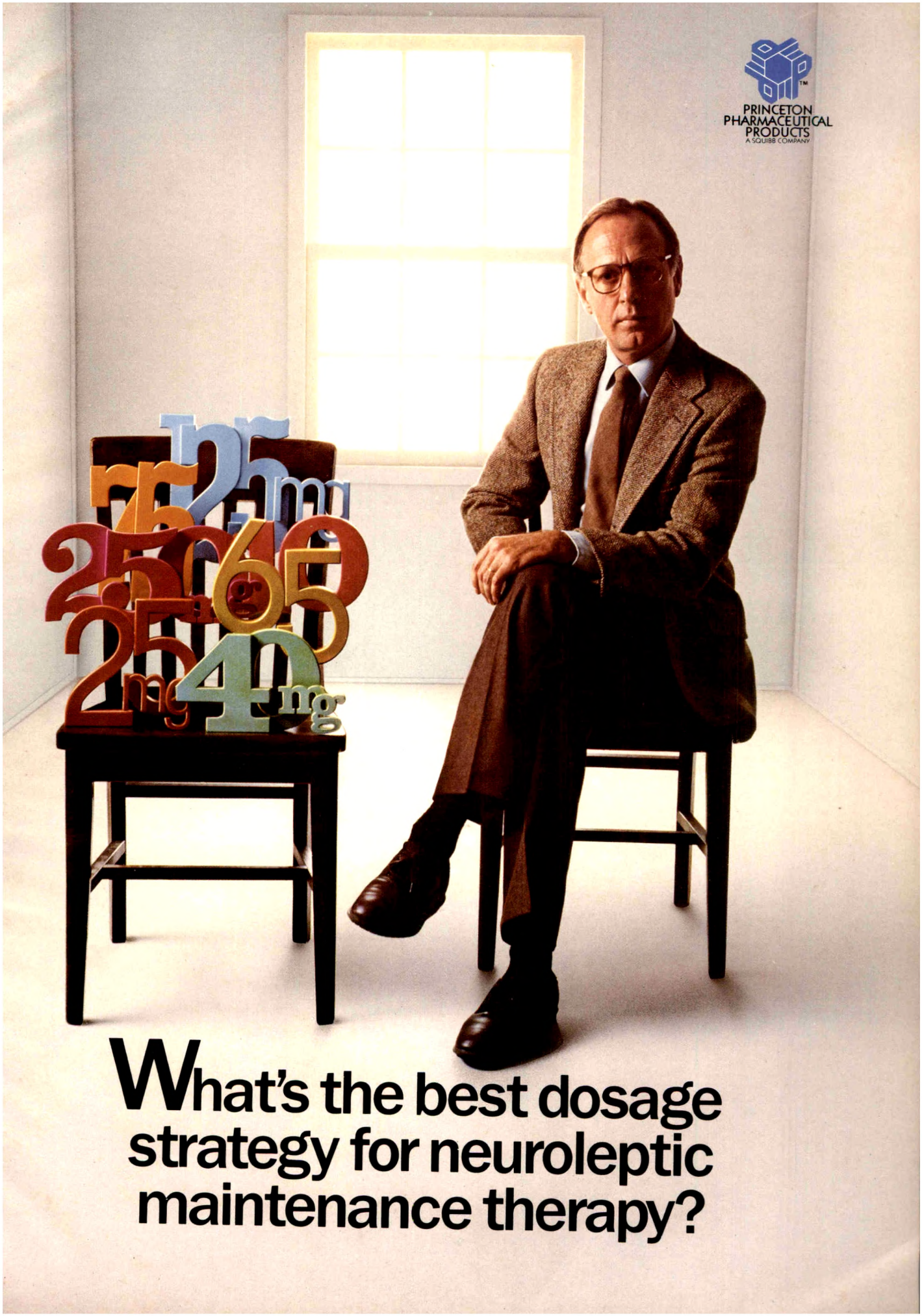
May 24-27, annual meeting, Association for the Care of Children's Health, Halifax, Nova Scotia, Canada. Contact Beverly H. Johnson, R.N., B.S.N., Executive Director, 3615 Wisconsin Ave., N.W., Washington, DC 20016; 202-244-1801.

May 24-28, annual meeting, American Association on Mental Deficiency, Los Angeles. Contact Albert J. Berkowitz, Ed.D., Executive Director, 1719 Kalorama Rd., N.W., Washington, DC 20009; 202-387-1968.

May 25-30, annual meeting, American Association of Suicidology, San Francisco. Contact Julie Perlman, M.S.W., Executive Officer, 2459 South Ash, Denver, CO 80222; 303-692-0985.

May 27-30, annual meeting, American College Health Association, Chicago. Contact Stephen D. Blom, Executive Director, 15879 Crabbs Branch Way, Rockville, MD 20855; 301-963-1100.

May 29-June 1, annual meeting, International Physicians for the Prevention of Nuclear War, Inc., Moscow. Contact Thomas C. Chalmers, M.D., Research Program Chairman, IPPNW, 225 Longwood Ave., Boston, MA 02115; 617-738-9404; Telex 4430017 IPPNW.



What's the best dosage strategy for neuroleptic maintenance therapy?

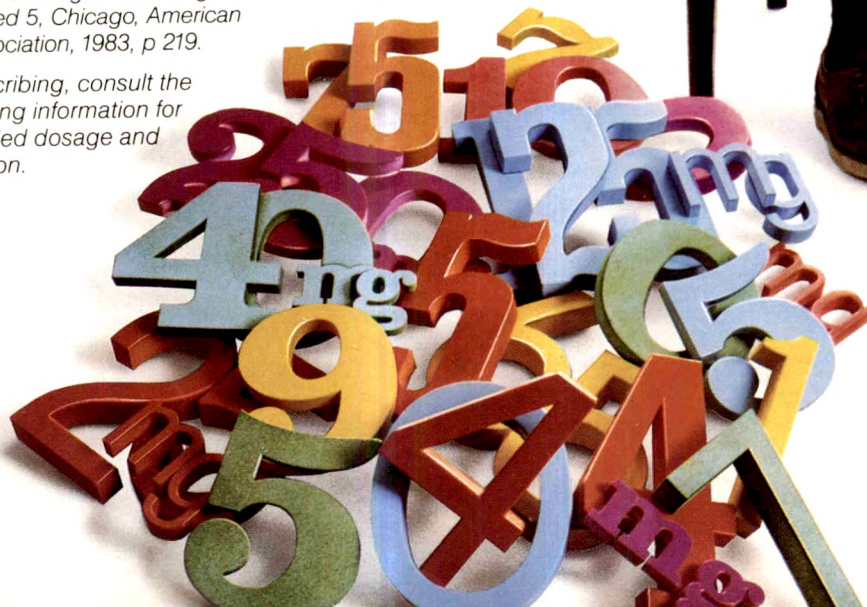
“The maintenance dose should be the minimum amount that maintains therapeutic response and allows the patient to function best.”*

Prescribe Low-Dose PROLIXIN® (fluphenazine hydrochloride)

**Many patients can be
maintained on
1 to 5 mg once a day†**

*AMA Division of Drugs: AMA drug evaluations, ed 5, Chicago, American Medical Association, 1983, p 219.

†Before prescribing, consult the full prescribing information for recommended dosage and administration.





Safe, effective treatment

Helps avoid side effects most commonly associated with low-potency neuroleptics*

- ▶ Less sedation¹
- ▶ Fewer anticholinergic effects²
- ▶ Less risk of cardiovascular effects²
- ▶ Rarely reported sexual dysfunction²

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The low-dose PROLIXIN® family of products offers continuity of care, with a dosage form for every need:

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**Lowering the dose,
lowering dose-related side effects**

* While the risk of extrapyramidal symptoms is increased with high-potency neuroleptics, these symptoms are usually dose-related and can generally be controlled by dosage adjustments.

Please see brief summary on last page of this advertisement.

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PROLIXIN® Tablets (fluphenazine hydrochloride tablets USP)

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DESCRIPTION: Prolixin Tablets (Fluphenazine Hydrochloride Tablets USP) provide 1, 2.5, 5, or 10 mg fluphenazine hydrochloride per tablet. Prolixin 2.5, 5, and 10 mg tablets contain FD&C Yellow No. 5 (tartrazine). Prolixin Elixir (Fluphenazine Hydrochloride Elixir USP) provides 0.5 mg fluphenazine hydrochloride per mL (2.5 mg per 5 mL teaspoonful) with 14% alcohol by volume. Prolixin Oral Concentrate (Fluphenazine Hydrochloride Oral Solution*) provides 5 mg fluphenazine hydrochloride per mL with 14% alcohol by volume (exceeds the USP monograph 1.2% limit). Prolixin Injection (Fluphenazine Hydrochloride Injection USP) provides 2.5 mg fluphenazine hydrochloride per mL; it contains 0.1% methylparaben and 0.01% propylparaben as preservatives. Prolixin Decanoate (Fluphenazine Decanoate Injection) provides 25 mg fluphenazine decanoate per mL in a sesame oil vehicle with 1.2% (w/v) benzyl alcohol as preservative.

CONTRAINDICATIONS: In the presence of suspected or established subcortical brain damage. In patients who have a blood dyscrasia or liver damage, or who are receiving large doses of hypnotics, or who are comatose or severely depressed. In patients who have shown hypersensitivity to fluphenazine; cross-sensitivity to phenothiazine derivatives may occur. Fluphenazine Decanoate is not intended for use in children under 12.

WARNINGS: Tardive Dyskinesia—potentially irreversible, involuntary, dyskinetic movements may develop. This syndrome appears to be most prevalent among the elderly, especially women; however, prevalence estimates do not reliably predict, at the inception of neuroleptic treatment, those patients likely to develop the syndrome. It is unknown if neuroleptics differ in their potential to cause tardive dyskinesia. The risk of developing the syndrome and the likelihood of its irreversibility are believed to increase as duration of treatment and cumulative dose increase. Although uncommon, the syndrome can develop after brief treatment at low doses. There is no known treatment for tardive dyskinesia, although partial or complete remission may occur with withdrawal of the neuroleptic. Neuroleptic treatment may suppress signs and symptoms of the syndrome and may mask the underlying disease process. The effect of symptomatic suppression on the long-term course of the syndrome is unknown. Neuroleptics should, thus, be prescribed with consideration for the potential of tardive dyskinesia. Chronic treatment should generally be reserved for patients with chronic illness that responds to neuroleptic drugs, and for whom alternative effective, less harmful treatments are not available or appropriate. Patients requiring chronic treatment should receive the smallest dose and shortest duration of treatment producing a satisfactory clinical response. Continuation of treatment should be reassessed periodically. If signs and symptoms of tardive dyskinesia appear, neuroleptic discontinuation should be considered. However, some patients may require continued treatment. (See PRECAUTIONS and ADVERSE REACTIONS.)

Mental and physical abilities required for driving a car or operating heavy machinery may be impaired by use of this drug. Potentiation of effects of alcohol may occur. Safety and efficacy in children have not been established because of inadequate experience in use in children. Severe adverse reactions, requiring immediate medical attention, may possibly occur.

Usage in Pregnancy: Safety for use during pregnancy has not been established; weigh possible hazards against potential benefits if administering any of these drugs to pregnant patients.

PRECAUTIONS: Caution must be exercised if another phenothiazine compound caused cholestatic jaundice, dermatoses or other allergic reactions because of the possibility of cross-sensitivity. Prolixin Tablets (Fluphenazine Hydrochloride Tablets USP) 2.5, 5, and 10 mg contain FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible individuals. Although the overall incidence of FD&C Yellow No. 5 (tartrazine) sen-

sitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity. When psychotic patients on large doses of a phenothiazine drug are to undergo surgery, hypotensive phenomena should be watched for; less anesthetics or central nervous system depressants may be required. Because of added anticholinergic effects, fluphenazine may potentiate the effects of atropine.

Use fluphenazine cautiously in patients exposed to extreme heat or phosphorus insecticides; in patients with a history of convulsive disorders, since grand mal convulsions have occurred; and in patients with special medical disorders, such as mitral insufficiency or other cardiovascular diseases and pheochromocytoma. Bear in mind that with prolonged therapy there is the possibility of liver damage, pigmentary retinopathy, lenticular and corneal deposits, and development of irreversible dyskinesia.

Neuroleptic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of neuroleptic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time.

Periodic checking of hepatic and renal functions and blood picture should be done. Monitor renal function of patients on long-term therapy; if BUN becomes abnormal, discontinue fluphenazine. "Silent pneumonias" are possible. Fluphenazine decanoate should be administered under the direction of a physician experienced in the clinical use of psychotropic drugs.

Information for Patients: It is likely that some patients exposed chronically to neuroleptics will develop tardive dyskinesia; full information should be given to all patients, if possible, who are candidates for chronic use. Informing patients and/or guardians must take into account clinical circumstances and patient competency.

Abrupt Withdrawal: In general, phenothiazines do not produce psychic dependence. However, gastritis, nausea and vomiting, dizziness, and tremulousness have been reported following abrupt cessation of high dose therapy; reports suggest that these symptoms can be reduced if concomitant antiparkinsonian agents are continued for several weeks after the phenothiazine is withdrawn.

ADVERSE REACTIONS: Central Nervous System: Extrapyramidal symptoms are most frequently reported. Most often these symptoms are reversible, but they may be persistent. They include pseudoparkinsonism, dystonia, dyskinesia, akathisia, oculogyric crises, opisthotonos, and hyperreflexia. Muscle rigidity sometimes accompanied by hyperthermia has been reported following use of fluphenazine decanoate. One can expect a higher incidence of such reactions with fluphenazine decanoate than with less potent piperazine derivatives or straight-chain phenothiazines. The incidence and severity of such reactions will depend more on individual patient sensitivity, but dosage level and patient age are also determinants. As these reactions may be alarming, the patient should be forewarned and reassured. These reactions can usually be controlled by administration of an antiparkinsonian drug such as benzotropine mesylate and by subsequent reduction in dosage.

Tardive Dyskinesia: See WARNINGS. Characterized by involuntary choreo-athetoid movements involving tongue, face, mouth, lips, or jaw (e.g., tongue protrusion, puffing cheeks, puckering mouth, chewing movements), trunk and extremities. Severity and degree of impairment vary widely. May become clinically recognizable either during treatment, dosage reduction, or treatment withdrawal. To facilitate early detection, reduce dosage periodically (if clinically possible) and observe for signs of the disorder, especially since neuroleptics may mask the signs of the syndrome.

References: 1. Baldessarini RJ: Drugs and the treatment of psychiatric disorders, in Gilman AG, Goodman LS (eds): The Pharmacological Basis of Therapeutics, ed 6. New York, Macmillan Publishing Co, Inc., 1980, p 415. 2. Mason AS, Granacher RP: Clinical Handbook of Antipsychotic Drug Therapy. New York, Brunner/Mazel, 1980, pp 203, 221, 239.

Rare occurrences of neuroleptic malignant syndrome (NMS) have been reported in patients on neuroleptic therapy. The syndrome is characterized by hyperthermia, muscular rigidity, autonomic instability (labile blood pressure, tachycardia, diaphoresis), akinesia, and altered consciousness, sometimes progressing to stupor or coma. Leukocytosis, elevated CPK, liver function abnormalities, and acute renal failure may also occur. Neuroleptic therapy should be discontinued immediately and vigorous symptomatic treatment implemented since the syndrome is potentially fatal.

Phenothiazine derivatives have been known to cause restlessness, excitement, or bizarre dreams; reactivation or aggravation of psychotic processes may be encountered. If drowsiness or lethargy occurs, the dosage may need to be reduced. Dosages, far in excess of the recommended amounts, may induce a catatonic-like state.

Autonomic Nervous System: Hypertension and fluctuations in blood pressure have been reported. Although hypotension is rarely a problem, patients with pheochromocytoma, cerebral vascular or renal insufficiency, or a severe cardiac reserve deficiency such as mitral insufficiency appear to be particularly prone to this reaction and should be observed carefully. Supportive measures including intravenous vasopressor drugs should be instituted immediately should severe hypotension occur; *Levarterenol Bitartrate Injection* is the most suitable drug; *epinephrine should not be used* since phenothiazine derivatives have been found to reverse its action. Nausea, loss of appetite, salivation, polyuria, perspiration, dry mouth, headache, and constipation may occur. Reducing or temporarily discontinuing the dosage will usually control these effects. Blurred vision, glaucoma, bladder paralysis, fecal impaction, paralytic ileus, tachycardia, or nasal congestion have occurred in some patients on phenothiazine derivatives.

Metabolic and Endocrine: Weight change, peripheral edema, abnormal lactation, gynecomastia, menstrual irregularities, false results on pregnancy tests, impotency in men and increased libido in women have occurred in some patients on phenothiazine therapy.

Allergic Reactions: Itching, erythema, urticaria, seborrhea, photosensitivity, eczema and exfoliative dermatitis have been reported with phenothiazines. The possibility of anaphylactoid reactions should be borne in mind.

Hematologic: Blood dyscrasias including leukopenia, agranulocytosis, thrombocytopenic or nonthrombocytopenic purpura, eosinophilia, and pancytopenia have been observed with phenothiazines. If soreness of the mouth, gums or throat, or any symptoms of upper respiratory infection occur and confirmatory leukocyte count indicates cellular depression, therapy should be discontinued and other appropriate measures instituted immediately.

Hepatic: Liver damage manifested by cholestatic jaundice, particularly during the first months of therapy, may occur; treatment should be discontinued. A cephalin flocculation increase, sometimes accompanied by alterations in other liver function tests, has been reported in patients who have had no clinical evidence of liver damage.

Others: Sudden deaths have been reported in hospitalized patients on phenothiazines. Previous brain damage or seizures may be predisposing factors. High doses should be avoided in known seizure patients. Shortly before death, several patients showed flare-ups of psychotic behavior patterns. Autopsy findings have usually revealed acute fulminating pneumonia or pneumonitis, aspiration of gastric contents, or intramyocardial lesions. Although not a general feature of fluphenazine, potentiation of central nervous system depressants such as opiates, analgesics, antihistamines, barbiturates and alcohol may occur.

Systemic lupus erythematosus-like syndrome, hypotension severe enough to cause fatal cardiac arrest, altered electrocardiographic and electroencephalographic tracings, altered cerebrospinal fluid proteins, cerebral edema, asthma, laryngeal edema, and angioneurotic edema; with long-term use, skin pigmentation, and lenticular and corneal opacities have occurred with phenothiazines. Local tissue reactions occur only rarely with injections of fluphenazine decanoate.

HOW SUPPLIED: Tablets—1 mg, 2.5 mg, 5 mg, and 10 mg in bottles of 50, 100 and 500, and in Unimatic® cartons of 100. Elixir—in bottles of 473 mL (1 pint) and in 60 mL dropper-assembly bottles with calibrated dropper. Oral Concentrate—in bottles of 120 mL with calibrated dropper. Injection—in multiple-dose vials of 10 mL. Fluphenazine Decanoate—in 1 mL Unimatic® single dose preassembled syringes and 5 mL vials.

For full prescribing information, consult package inserts. (J4-120/147/153/150)

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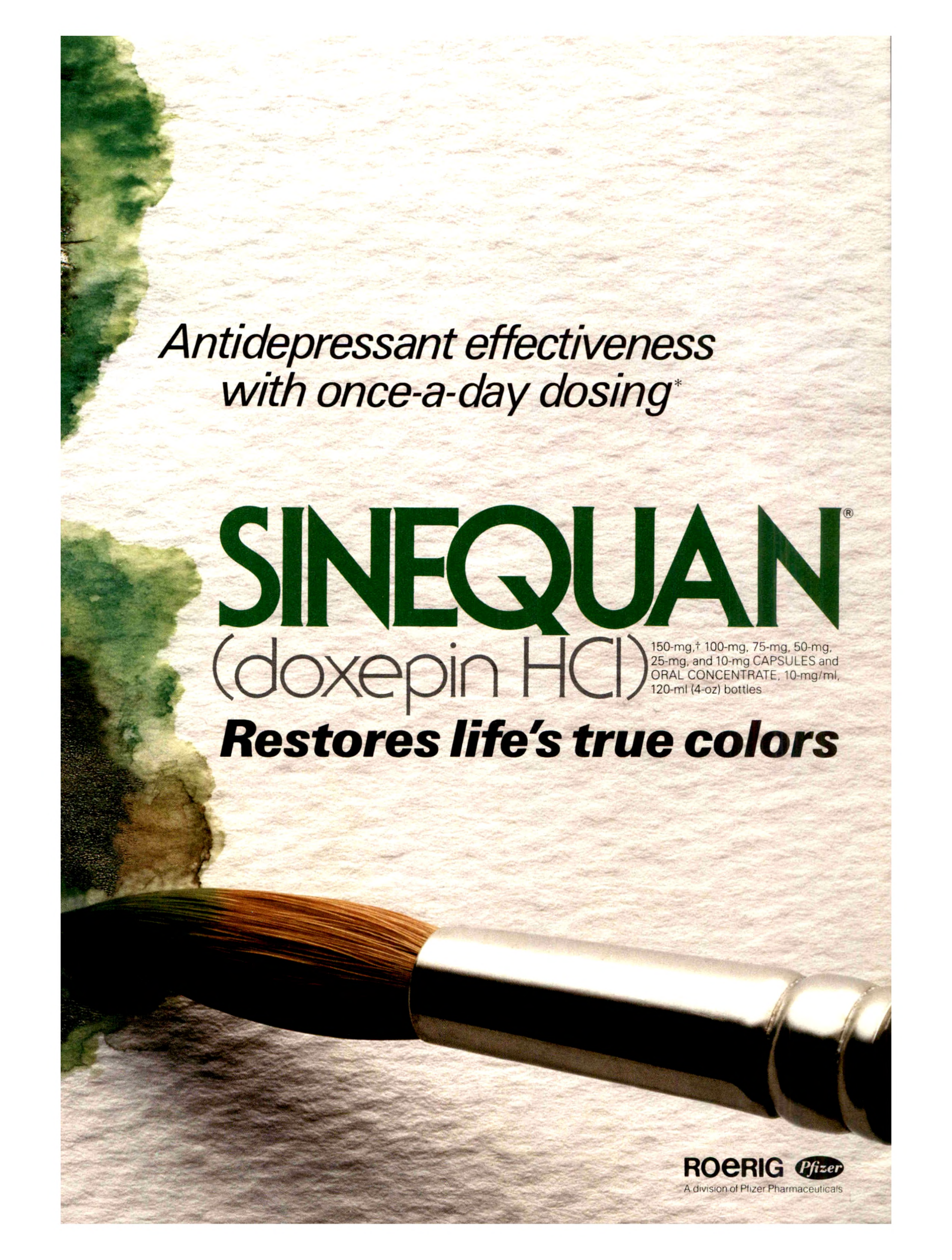
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*The total daily dosage of Sinequan may be given on a divided or once-a-day dosage schedule. If the once-a-day schedule is employed, the maximum recommended dose is 150 mg. This dose may be given at bedtime.
†The 150-mg capsule strength is intended for maintenance therapy only and is not recommended for initiation of treatment.

For a brief summary of SINEQUAN prescribing information including adverse reactions, please see the following page of this advertisement.



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SINEQUAN[®] (doxepin HCl)

BRIEF SUMMARY

SINEQUAN[®] (doxepin HCl) Capsules/Oral Concentrate

Contraindications. SINEQUAN is contraindicated in individuals who have shown hypersensitivity to the drug. Possibility of cross sensitivity with other dibenzoxepines should be kept in mind.

SINEQUAN is contraindicated in patients with glaucoma or a tendency to urinary retention. These disorders should be ruled out, particularly in older patients.

Warnings. The once-a-day dosage regimen of SINEQUAN in patients with intercurrent illness or patients taking other medications should be carefully adjusted. This is especially important in patients receiving other medications with anticholinergic effects.

Usage in Geriatrics: The use of SINEQUAN on a once-a-day dosage regimen in geriatric patients should be adjusted carefully based on the patient's condition.

Usage in Pregnancy: Reproduction studies have been performed in rats, rabbits, monkeys and dogs and there was no evidence of harm to the animal fetus. The relevance to humans is not known. Since there is no experience in pregnant women who have received this drug, safety in pregnancy has not been established. There are no data with respect to the secretion of the drug in human milk and its effect on the nursing infant.

Usage in Children: The use of SINEQUAN in children under 12 years of age is not recommended because safe conditions for its use have not been established.

MAO Inhibitors: Serious side effects and even death have been reported following the concomitant use of certain drugs with MAO inhibitors. Therefore, MAO inhibitors should be discontinued at least two weeks prior to the cautious initiation of therapy with SINEQUAN. The exact length of time may vary and is dependent upon the particular MAO inhibitor being used, the length of time it has been administered, and the dosage involved.

Usage with Alcohol: It should be borne in mind that alcohol ingestion may increase the danger inherent in any intentional or unintentional SINEQUAN overdosage. This is especially important in patients who may use alcohol excessively.

Precautions. Since drowsiness may occur with the use of this drug, patients should be warned of the possibility and cautioned against driving a car or operating dangerous machinery while taking the drug. Patients should also be cautioned that their response to alcohol may be potentiated.

Since suicide is an inherent risk in any depressed patient and may remain so until significant improvement has occurred, patients should be closely supervised during the early course of therapy. Prescriptions should be written for the smallest feasible amount.

Should increased symptoms of psychosis or shift to manic symptomatology occur, it may be necessary to reduce dosage or add a major tranquilizer to the dosage regimen.

Adverse Reactions. NOTE: Some of the adverse reactions noted below have not been specifically reported with SINEQUAN use. However, due to the close pharmacological similarities among the tricyclics, the reactions should be considered when prescribing SINEQUAN.

Anticholinergic Effects: Dry mouth, blurred vision, constipation, and urinary retention have been reported. If they do not subside with continued therapy, or become severe, it may be necessary to reduce the dosage.

Central Nervous System Effects: Drowsiness is the most commonly noticed side effect. This tends to disappear as therapy is continued. Other infrequently reported CNS side effects are confusion, disorientation, hallucinations, numbness, paresthesias, ataxia, and extrapyramidal symptoms and seizures.

Cardiovascular: Cardiovascular effects including hypotension and tachycardia have been reported occasionally.

Allergic: Skin rash, edema, photosensitization, and pruritus have occasionally occurred.

Hematologic: Eosinophilia has been reported in a few patients. There have been occasional reports of bone marrow depression manifesting as agranulocytosis, leukopenia, thrombocytopenia, and purpura.

Gastrointestinal: Nausea, vomiting, indigestion, taste disturbances, diarrhea, anorexia, and aphthous stomatitis have been reported. (See anticholinergic effects.)

Endocrine: Stained or lowered libido, testicular swelling, gynecomastia in males, enlargement of breasts and galactorrhea in the female, raising or lowering of blood sugar levels, and syndrome of inappropriate antidiuretic hormone have been reported with tricyclic administration.

Other: Dizziness, tinnitus, weight gain, sweating, chills, fatigue, weakness, flushing, jaundice, alopecia, and headache have been occasionally observed as adverse effects.

Withdrawal Symptoms: The possibility of development of withdrawal symptoms upon abrupt cessation of treatment after prolonged SINEQUAN administration should be borne in mind. These are not indicative of addiction and gradual withdrawal of medication should not cause these symptoms.

Dosage and Administration. For most patients with illness of mild to moderate severity, a starting daily dose of 75 mg is recommended. Dosage may subsequently be increased or decreased at appropriate intervals and according to individual response. The usual optimum dose range is 75 mg/day to 150 mg/day.

In more severely ill patients higher doses may be required with subsequent gradual increase to 300 mg/day if necessary. Additional therapeutic effect is rarely to be obtained by exceeding a dose of 300 mg/day.

In patients with very mild symptomatology or emotional symptoms accompanying organic disease, lower doses may suffice. Some of these patients have been controlled on doses as low as 25-50 mg/day.

The total daily dosage of SINEQUAN may be given on a divided or once-a-day dosage schedule. If the once-a-day schedule is employed the maximum recommended dose is 150 mg/day. This dose may be given at bedtime. **The 150 mg capsule strength is intended for maintenance therapy only and is not recommended for initiation of treatment.**

Anti-anxiety effect is apparent before the antidepressant effect. Optimal antidepressant effect may not be evident for two to three weeks.

Overdosage.

A. Signs and Symptoms

1. Mild: Drowsiness, stupor, blurred vision, excessive dryness of mouth.
2. Severe: Respiratory depression, hypotension, coma, convulsions, cardiac arrhythmias and tachycardias.

Also: urinary retention (bladder atony), decreased gastrointestinal motility (paralytic ileus), hyperthermia (or hypothermia), hypertension, dilated pupils, hyperactive reflexes.

B. Management and Treatment

1. Mild: Observation and supportive therapy is all that is usually necessary.
2. Severe: Medical management of severe SINEQUAN overdosage consists of aggressive supportive therapy. If the patient is conscious, gastric lavage, with appropriate precautions to prevent pulmonary aspiration, should be performed even though SINEQUAN is rapidly absorbed. The use of activated charcoal has been recommended, as has been continuous gastric lavage with saline for 24 hours or more. An adequate airway should be established in comatose patients and assisted ventilation used if necessary. EKG monitoring may be required for several days, since relapse after apparent recovery has been reported. Arrhythmias should be treated with the appropriate antiarrhythmic agent. It has been reported that many of the cardiovascular and CNS symptoms of tricyclic antidepressant poisoning in adults may be reversed by the slow intravenous administration of 1 mg to 3 mg of physostigmine salicylate. Because physostigmine is rapidly metabolized, the dosage should be repeated as required. Convulsions may respond to standard anticonvulsant therapy; however, barbiturates may potentiate any respiratory depression. Dialysis and forced diuresis generally are not of value in the management of overdosage due to high tissue and protein binding of SINEQUAN.

More detailed professional information available on request.

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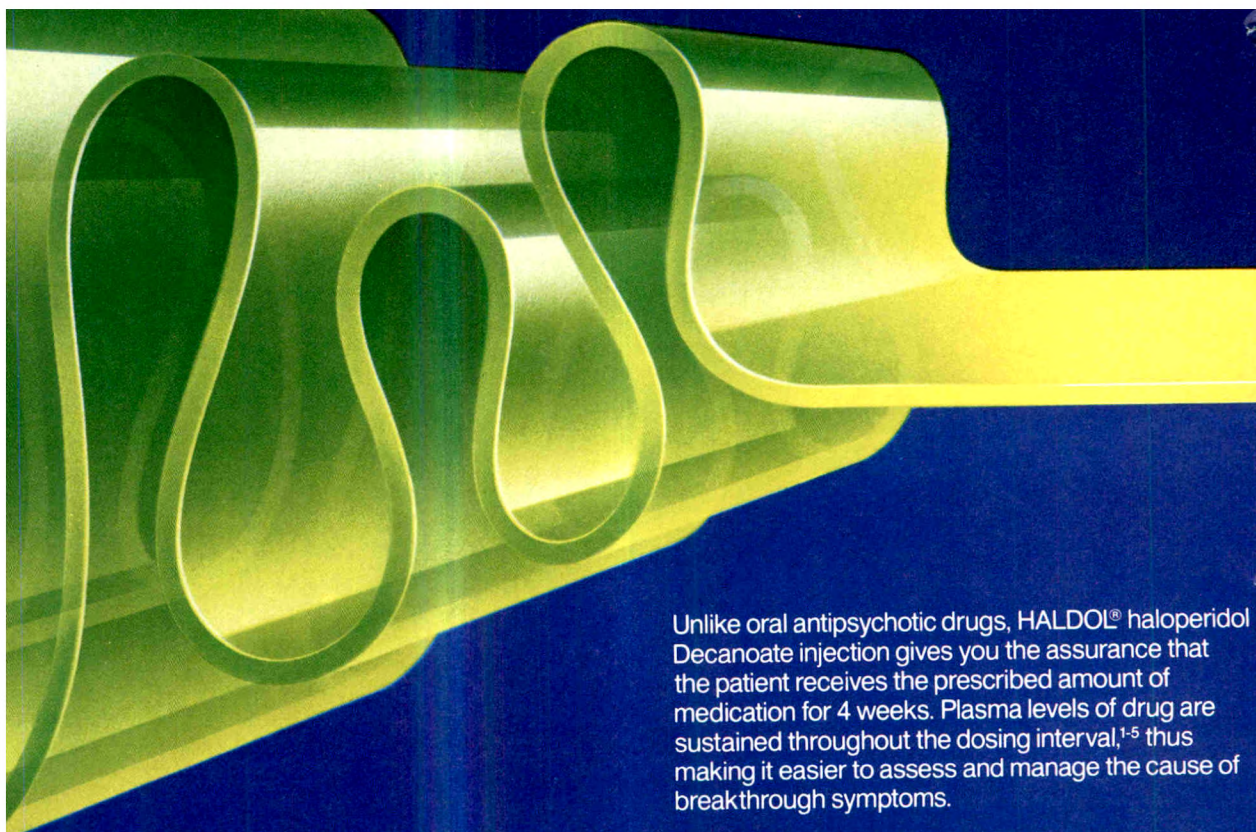
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a single monthly dose**

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the therapeutic constant in schizophrenia

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The side effects of HALDOL Decanoate are those of HALDOL. The prolonged action of HALDOL Decanoate should be considered in the management of side effects. During dose adjustment or episodes of exacerbation of psychotic symptoms, HALDOL Decanoate therapy can be supplemented with short-acting forms of HALDOL. It is recommended that patients being considered for HALDOL Decanoate therapy be initially converted to oral HALDOL (from whatever other neuroleptic they are taking) in order to exclude the possibility of an unexpected adverse sensitivity to haloperidol. HALDOL Decanoate is administered only by deep intramuscular injection.

Offers sustained protection against schizophrenic relapse

Dependable delivery with HALDOL Decanoate helps provide protection for your patient to withstand the demands of daily life.

References

1. Nair NPV, Suranyi-Cadotte B, Schwartz G, et al: A clinical trial comparing intramuscular haloperidol decanoate and oral haloperidol in chronic schizophrenic patients: Efficacy, safety, and dosage equivalence. *J Clin Psychopharmacol* 1986;6(No. 1, Suppl.):30S-37S.
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Please see brief summary of prescribing information on next page.

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HALDOL DECANOATE (HALOPERIDOL) INJECTION

The following is a brief summary only. Before prescribing, see complete prescribing information in HALDOL and HALDOL Decanoate product labeling.

Contraindications: Since the pharmacologic and clinical actions of HALDOL (haloperidol) Decanoate are attributed to HALDOL as the active medication, Contraindications, Warnings, and additional information are those of HALDOL. Some sections have been modified to reflect the prolonged action of HALDOL Decanoate.

HALDOL is contraindicated in severe toxic central nervous system depression or comatose states from any cause and in individuals who are hypersensitive to this drug or have Parkinson's disease.

Warnings: *Tardive Dyskinesia:* Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown. Both the risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown. Given these considerations, antipsychotic drugs should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that 1) is known to respond to antipsychotic drugs, and 2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically. If signs and symptoms of tardive dyskinesia appear in a patient on antipsychotics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome. (For further information about the description of tardive dyskinesia and its clinical detection, please refer to ADVERSE REACTIONS.)

Usage in Pregnancy: (see PRECAUTIONS - Usage in Pregnancy) **Combined Use With Lithium:** (see PRECAUTIONS - Drug Interactions).

General: Bronchopneumonia, sometimes fatal, has followed use of antipsychotic drugs, including haloperidol. Prompt remedial therapy should be instituted if dehydration, hemoconcentration or reduced pulmonary ventilation occur, especially in the elderly. Decreased serum cholesterol and/or cutaneous and ocular changes have been reported with chemically-related drugs, although not with haloperidol. See PRECAUTIONS - Information for Patients for information on mental and/or physical abilities and on concomitant use with other substances.

Precautions: Administer cautiously to patients: (1) with severe cardiovascular disorders, due to the possibility of transient hypotension and/or precipitation of anginal pain (if a vasopressor is required, epinephrine should not be used since HALDOL may block its vasopressor activity and paradoxical further lowering of blood pressure may occur; metaraminol, phenylephrine or norepinephrine should be used); (2) receiving anticonvulsant medications, with a history of seizures, or with EEG abnormalities, because HALDOL may lower the convulsive threshold. If indicated, adequate anticonvulsant therapy should be concomitantly maintained; (3) with known allergies or a history of allergic reactions to drugs; (4) receiving anticoagulants, since an isolated instance of interference occurred with the effects of one anticoagulant (phenindione). Concomitant antiparkinson medication, if required, may have to be continued after HALDOL is discontinued because of different excretion rates; if both are discontinued simultaneously, extrapyramidal symptoms may occur. Intraocular pressure may increase when anticholinergic drugs, including antiparkinson drugs, are administered concomitantly with HALDOL. When HALDOL is used for mania in bipolar disorders, there may be a rapid mood swing to depression. Severe neurotoxicity may occur in patients with thyrotoxicosis receiving antipsychotic medication, including HALDOL.

The 1, 5 and 10 mg HALDOL tablets contain FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible individuals, especially in those who have aspirin hypersensitivity.

Information for Patients: Mental and/or physical abilities required for hazardous tasks or driving may be impaired. Alcohol should be avoided due to possible additive effects and hypotension.

Drug Interactions: Patients receiving lithium plus haloperidol should be monitored closely for early evidence of neurological toxicity and treatment discontinued promptly if such signs appear.

Carcinogenesis, Mutagenesis and Impairment of Fertility: No mutagenic potential of haloperidol decanoate was found in the Ames Salmonella microsome activation assay.

Carcinogenicity studies using oral haloperidol were conducted in Wistar rats (dosed at up to 5 mg/kg daily for 24 months) and in Albino Swiss mice (dosed at up to 5 mg/kg daily for 18 months). In the rat study survival was less than optimal in all dose groups, reducing the number of rats at risk for developing tumors. However, although a relatively greater number of rats survived to the end of the study in high dose male and female groups, these animals did not have a greater incidence of tumors than control animals. Therefore, although not optimal, this study does suggest the absence of a haloperidol related increase in the incidence of neoplasia

in rats at doses up to 20 times the usual daily human dose for chronic or resistant patients. In female mice at 5 and 20 times the highest initial daily dose for chronic or resistant patients, there was a statistically significant increase in mammary gland neoplasia and total tumor incidence; at 20 times the same daily dose there was a statistically significant increase in pituitary gland neoplasia. In male mice, no statistically significant differences in incidences of total tumors or specific tumor types were noted.

Antipsychotic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of antipsychotic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time.

Usage in Pregnancy: Pregnancy Category C. Safe use in pregnancy or in women likely to become pregnant has not been established; use only if benefit clearly justifies potential hazards to the fetus.

Nursing Mothers: Infants should not be nursed during drug treatment.

Pediatric Use: Controlled trials to establish the safety and effectiveness of intramuscular administration in children have not been conducted.

Adverse Reactions: Adverse reactions following the administration of HALDOL (haloperidol) Decanoate are those of HALDOL. Since vast experience has accumulated with HALDOL, the adverse reactions are reported for that compound as well as for HALDOL Decanoate. As with all injectable medications, local tissue reactions have been reported with HALDOL Decanoate.

CNS Effects: Extrapyramidal Reactions—Neuromuscular (extrapyramidal) reactions have been reported frequently, often during the first few days of treatment. Generally they involved Parkinson-like symptoms which when first observed were usually mild to moderately severe and usually reversible. Other types of neuromuscular reactions (motor restlessness, dystonia and tardive dyskinesia, akathisia, hyperreflexia, opisthotonos, oculogyric crises) have been reported far less frequently, but were often more severe. Severe extrapyramidal reactions have been reported at relatively low doses. Generally, extrapyramidal symptoms are dose-related since they occur at relatively high doses and disappear or become less severe when the dose is reduced. Antiparkinson drugs may be required. Persistent extrapyramidal reactions have been reported and the drug may have to be discontinued in such cases. **Withdrawal Emergent Neurological Signs—**Abrupt discontinuation of short-term antipsychotic therapy is generally uneventful. However, some patients on maintenance treatment experience transient dyskinetic signs after abrupt withdrawal. In certain cases these are indistinguishable from "tardive dyskinesia" except for duration. It is unknown whether gradual withdrawal will reduce the occurrence of these signs, but until further evidence is available HALDOL should be gradually withdrawn. **Tardive Dyskinesia—**As with all antipsychotic agents HALDOL has been associated with persistent dyskinesias. Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may appear in some patients on long-term therapy or may occur after drug therapy has been discontinued. The risk appears to be greater in elderly patients on high-dose therapy, especially females. The symptoms are persistent and in some patients appear irreversible. The syndrome is characterized by rhythmical involuntary movements of tongue, face, mouth or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities and the trunk. There is no known effective treatment for tardive dyskinesia; antiparkinson agents usually do not alleviate the symptoms of this syndrome. It is suggested that all antipsychotic agents be discontinued if these symptoms appear. Should it be necessary to reinstitute treatment, or increase the dosage of the agent, or switch to a different antipsychotic agent, this syndrome may be masked. It has been reported that fine vermicular movement of the tongue may be an early sign of tardive dyskinesia and if the medication is stopped at that time the full syndrome may not develop. **Other CNS Effects:** Insomnia, restlessness, anxiety, euphoria, agitation, drowsiness, depression, lethargy, headache, confusion, vertigo, grand mal seizures, and exacerbation of psychotic symptoms including hallucinations, and catatonic-like behavioral states which may be responsive to drug withdrawal and/or treatment with anticholinergic drugs.

Body as a Whole: Neuroleptic Malignant Syndrome: As with other antipsychotic drugs, a symptom complex sometimes referred to as neuroleptic malignant syndrome (NMS) has been reported. Cardinal features of NMS are hyperpyrexia, muscle rigidity, altered mental status (including catatonic signs), and evidence of autonomic instability (irregular pulse or blood pressure). Additional signs may include elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. NMS is potentially fatal, requires intensive symptomatic treatment and immediate discontinuation of antipsychotic treatment. Hyperpyrexia and heat stroke, not associated with the above symptom complex, have also been reported. **Cardiovascular Effects:** Tachycardia, hypotension, hypertension and ECG changes. **Hematologic Effects:** Reports of mild, usually transient leukopenia and leukocytosis, minimal decreases in red blood cell counts, anemia, or a tendency toward lymphomonocytosis; agranulocytosis rarely reported and only in association with other medication. **Liver Effects:** Impaired liver function and/or jaundice. **Dermatologic Reactions:** Maculopapular and acneiform reactions, isolated cases of photosensitivity, loss of hair. **Endocrine Disorders:** Lactation, breast engorgement, mastalgia, menstrual irregularities, gynecomastia, impotence, increased libido, hyperglycemia, hypoglycemia and hyponatremia. **Gastrointestinal Effects:** Anorexia, constipation, diarrhea, hypersalivation, dyspepsia, nausea and vomiting. **Autonomic Reactions:** Dry mouth, blurred vision, urinary retention, diaphoresis, and priapism. **Respiratory Effects:** Laryngospasm, bronchospasm and increased depth of respiration. **Special Senses:** Cataracts, retinopathy and visual disturbances. **Other:** Cases of sudden and unexpected death have been reported in association with the administration of HALDOL. The nature of the evidence makes it impossible to determine definitively what role, if any, HALDOL played in the outcome of the reported cases. The possibility that HALDOL caused death cannot, of course, be excluded, but it is to be kept in mind that sudden and unexpected death may occur in psychotic patients when they go untreated or when they are treated with other antipsychotic drugs.

IMPORTANT: Full directions for use should be read before HALDOL or HALDOL Decanoate is administered or prescribed.

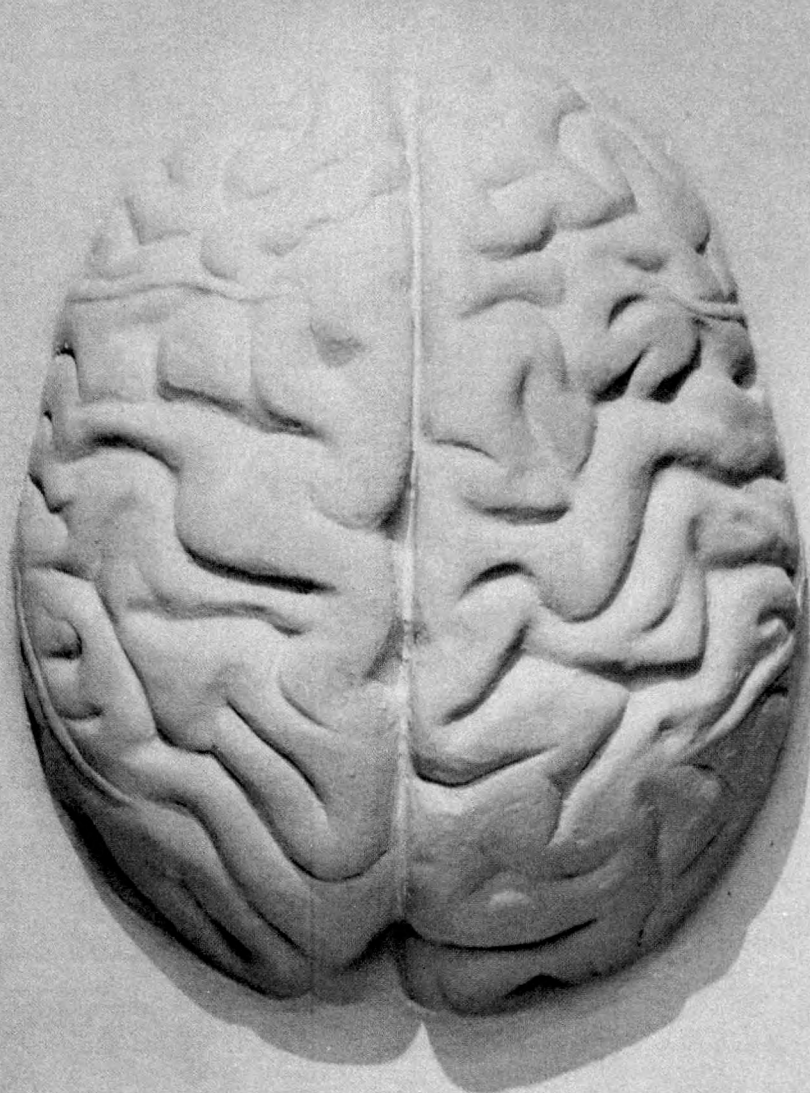
For information on symptoms and treatment of overdose, see full prescribing information.

The short-acting HALDOL injectable form is intended only for acutely agitated psychotic patients with moderately severe to very severe symptoms.

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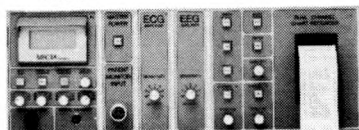
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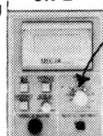
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Indications: Management of anxiety disorders; short-term relief of anxiety symptoms, acute alcohol withdrawal symptoms, preoperative apprehension and anxiety. Usually not required for anxiety or tension associated with stress of everyday life. Efficacy beyond four months not established by systematic clinical studies. Periodic reassessment of therapy recommended.

Contraindications: Known hypersensitivity to the drug.

Warnings: Warn patients that mental and/or physical abilities required for tasks such as driving or operating machinery may be impaired, as may be mental alertness in children, and that concomitant use with alcohol or CNS depressants may have an additive effect. Though physical and psychological dependence have rarely been reported on recommended doses, use caution in administering to addiction-prone individuals or those who might increase dosage. Withdrawal symptoms (including convulsions) reported after abrupt cessation of extended use of excessive doses are similar to those seen with barbiturates. Milder symptoms reported infrequently when continuous therapy is abruptly ended. Avoid abrupt discontinuation; gradually taper dosage.

Usage in Pregnancy: Use of minor tranquilizers during the first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.

Precautions: In the elderly and debilitated, and in children over six, limit to smallest effective dosage (initially 10 mg or less per day) to preclude ataxia or oversedation, increasing gradually as needed and tolerated. Not recommended in children under six. Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider individual pharmacologic effects, particularly in use of potentiating drugs such as MAO inhibitors and phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions (e.g., excitement, stimulation and acute rage) have been reported in psychiatric patients and hyperactive aggressive children. Employ usual precautions in treatment of anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation have been reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship has not been established clinically. Due to isolated reports of exacerbation, use with caution in patients with porphyria.

Adverse Reactions: Drowsiness, ataxia and confusion may occur, especially in the elderly and debilitated. These are reversible in most instances by proper dosage adjustment, but are also occasionally observed at the lower dosage ranges. In a few instances syncope has been reported. Also encountered are isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent and generally controlled with dosage reduction; changes in EEG patterns (low-voltage fast activity) may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice and hepatic dysfunction have been reported occasionally, making periodic blood counts and liver function tests advisable during protracted therapy.

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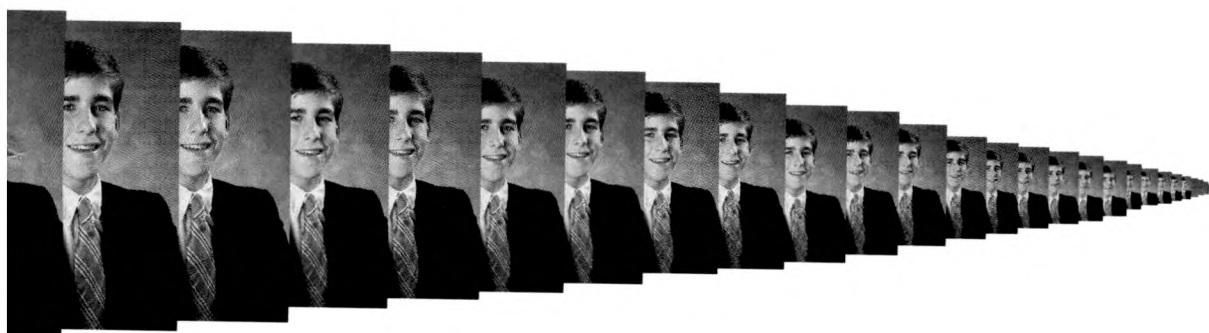
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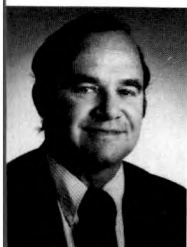
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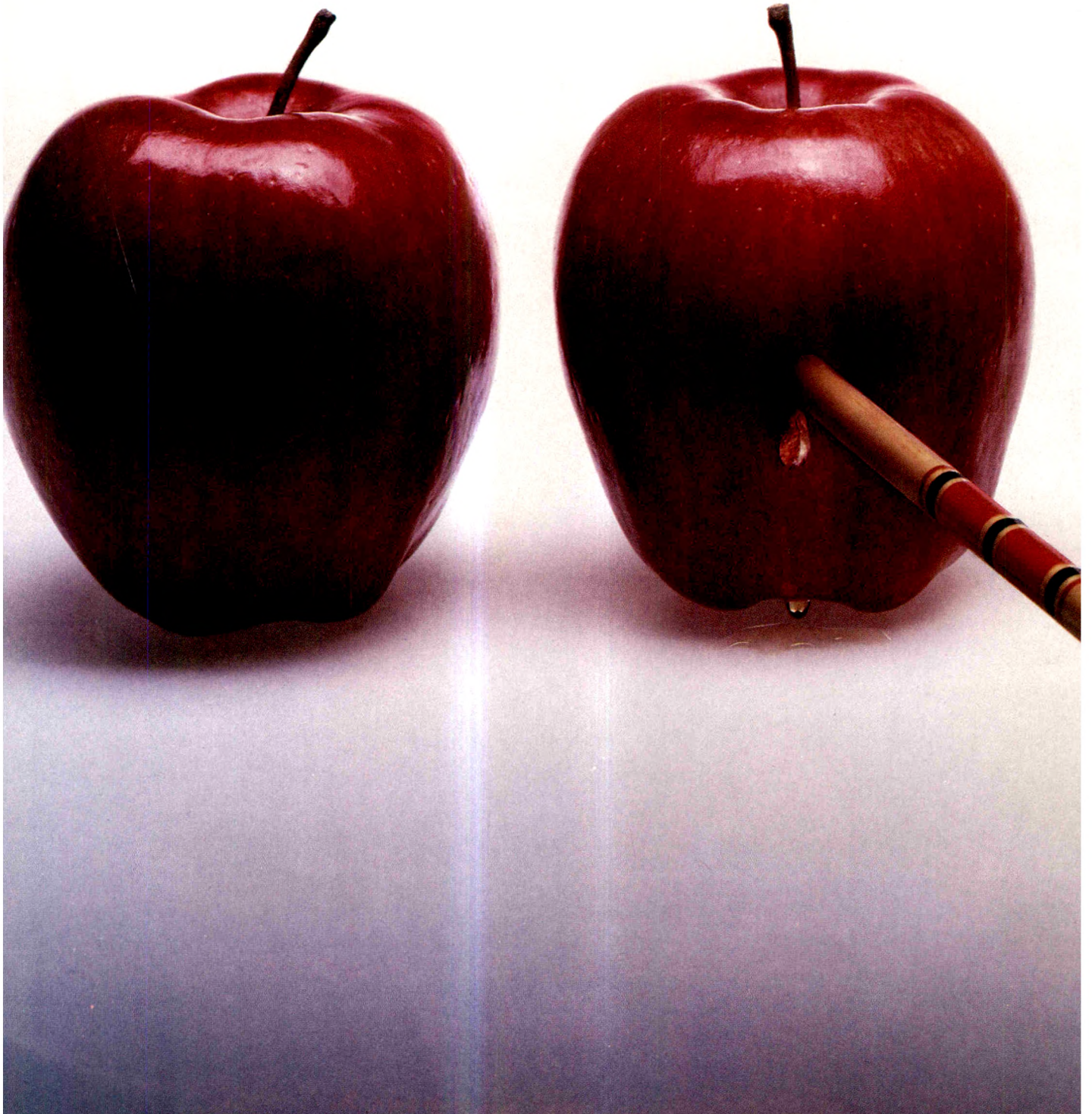
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INDICATIONS: LOXITANE is indicated for the management of the manifestations of psychotic disorders. The antipsychotic efficacy of LOXITANE was established in clinical studies which enrolled newly hospitalized and chronically hospitalized acutely ill schizophrenic patients as subjects.

CONTRAINDICATIONS: Comatose or severe drug-induced depressed states (alcohol, barbiturates, narcotics, etc.); hypersensitivity to the dibenzoxazepines.

WARNINGS: *Tardive Dyskinesia:* Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may develop in patients treated with neuroleptic (antipsychotic) drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of neuroleptic treatment, which patients are likely to develop the syndrome. Whether neuroleptic drug products differ in their potential to cause tardive dyskinesia is unknown.

Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dosage of neuroleptic drugs administered to the patient increases. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low dosages.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if neuroleptic treatment is withdrawn. Neuroleptic treatment itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome, and thereby may possibly mask the underlying disease process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, neuroleptics should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic neuroleptic treatment should generally be reserved for patients who suffer from a chronic illness that (1) is known to respond to neuroleptic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dosage and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on neuroleptics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome.

Mental and/or physical abilities may be impaired, especially during early therapy; warn ambulatory patients about activities requiring alertness, about concomitant use of alcohol and other CNS depressants. Not recommended for management of behavioral complications in mentally retarded patients.

PRECAUTIONS: Use with extreme caution in patients with a history of convulsive disorders; seizures have been reported in epileptic patients receiving antipsychotic dosage levels and in epileptic patients with maintenance of anticonvulsant therapy. Use with caution in patients with cardiovascular disease or in those with glaucoma or a tendency to urinary retention, particularly when on concomitant anticholinergic medication. Loxapine has an antiemetic effect in animals which might occur in man, masking signs of overdosage of toxic drugs and obscuring intestinal obstruction or brain tumor. Since possible ocular toxicity cannot be excluded, observe carefully for pigmentary retinopathy and lenticular pigmentation. Slightly higher incidence of extrapyramidal effects possible following IM administration than normally anticipated with oral formulations.

Neuroleptic drugs elevate prolactin levels; elevation persists during chronic administration. Tissue culture experiments indicate that approximately one third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of neuroleptic drugs. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time.

Safe use during pregnancy or lactation or by women of child-bearing potential has not been established; weigh potential benefits against possible risks to mother and child. No embryotoxicity or teratogenicity was observed in studies in rats, rabbits, or dogs, although, with the exception of one rabbit study, the highest dosage was only two times the maximum recommended human dosage, and in some studies it was below this dosage. Perinatal studies have shown renal papillary abnormalities in offspring of rats treated from midpregnancy with doses of 0.6 to 1.8 mg/kg doses which approximate the usual human dose but which are considerably below the maximum recommended human dose. It is known that this drug and its metabolites have been transported into the milk of lactating dogs. LOXITANE[®] loxapine administration to nursing women should be avoided, if clinically possible. Not recommended for use in children under 16.

ADVERSE REACTIONS: *CNS Effects:* Other than extrapyramidal, have been seen infrequently. Drowsiness, dizziness, faintness, staggering gait, muscle twitching, weakness, insomnia, agitation, tension, seizures, akinesia, slurred speech, numbness, and confusional states have been reported. Neuroleptic malignant syndrome (NMS) has been reported. *Extrapyramidal Reactions:* Neuromuscular (extrapyramidal) frequently, often during the first few days of treatment. Reactions involved parkinsonian-like symptoms such as tremor, rigidity, excessive salivation, and masked facies. Akathisia (motor restlessness) also has been reported relatively frequently. Dystonic and dyskinetic reactions have occurred less frequently, but may be more severe. Dystonias include spasms of muscles of the neck and face, tongue protrusion, and oculogyric movement. Dyskinetic reactions have been described in the form of choreoathetoid movements. These reactions sometimes require reduction or temporary withdrawal of loxapine dosage in addition to appropriate counteractive drugs.

Persistent Tardive Dyskinesia: As with all antipsychotic agents, tardive dyskinesia may appear in some patients on long-term therapy or may appear after drug therapy has been discontinued. Risk appears to be especially greater in elderly female patients on high-dosage therapy. Symptoms are persistent and in some patients appear to be irreversible. Syndrome is characterized by rhythmic involuntary movement of the tongue, face, mouth, or jaw (eg, protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities. *Cardiovascular Effects:* Tachycardia, hypotension, hypertension, orthostatic hypotension, lightheadedness, and syncope. A few cases of ECG changes have been reported. *Hematologic:* Rarely, agranulocytosis, thrombocytopenia, leukopenia. *Skin:* Dermatitis, edema (puffiness of face), pruritus, rash, alopecia, and seborrhea. *Anticholinergic Effects:* Dry mouth, nasal congestion, constipation, blurred vision, urinary retention, and paralytic ileus. *Gastrointestinal:* Nausea, vomiting, and hepatocellular injury (ie, SGOT/SGPT elevation). Rarely, jaundice and/or hepatitis. *Other:* Weight gain, weight loss, dyspnea, ptosis, hyperpyrexia, flushed facies, headache, paresthesia, and polydipsia. Rarely, galactorrhea, amenorrhea, gynecomastia, and menstrual irregularity of uncertain etiology.

OVERDOSAGE: Signs and symptoms are those expected from the pharmacological actions and amount ingested. Can range from mild depression of CNS and cardiovascular symptoms to profound hypotension, respiratory depression and unconsciousness. Extrapyramidal symptoms and convulsive seizures have occurred as well as renal failure. Treatment is essentially symptomatic and supportive. Early gastric lavage with dialysis might be expected to be beneficial. Avoid use of centrally acting emetics, analeptics, and epinephrine.

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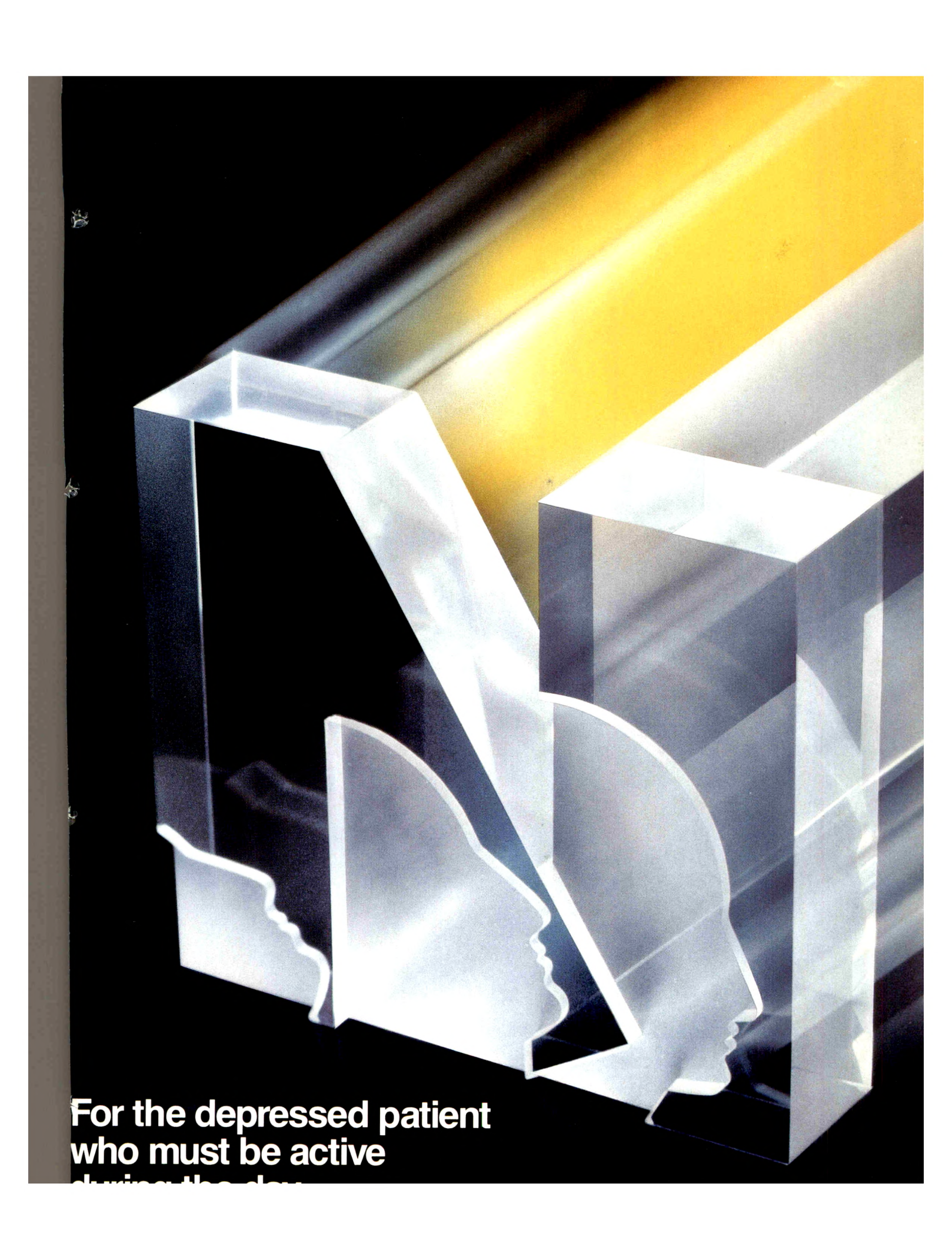
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2. Rhoades HM, Overall JE: Side effect potentials of different antipsychotic and antidepressant drugs. *Psychopharmacol Bull* 1984; 20:83-88.
3. Data on file, Lederle Laboratories, Pearl River, N.Y.

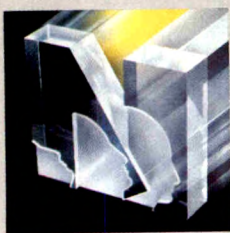
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An abstract geometric sculpture composed of white, angular, box-like structures. A bright yellow, curved, translucent element is positioned at the top, casting a strong light across the scene. The white structures are interconnected, with some featuring jagged, sawtooth-like edges. The background is dark, creating a high-contrast environment. The overall composition is dynamic and architectural.

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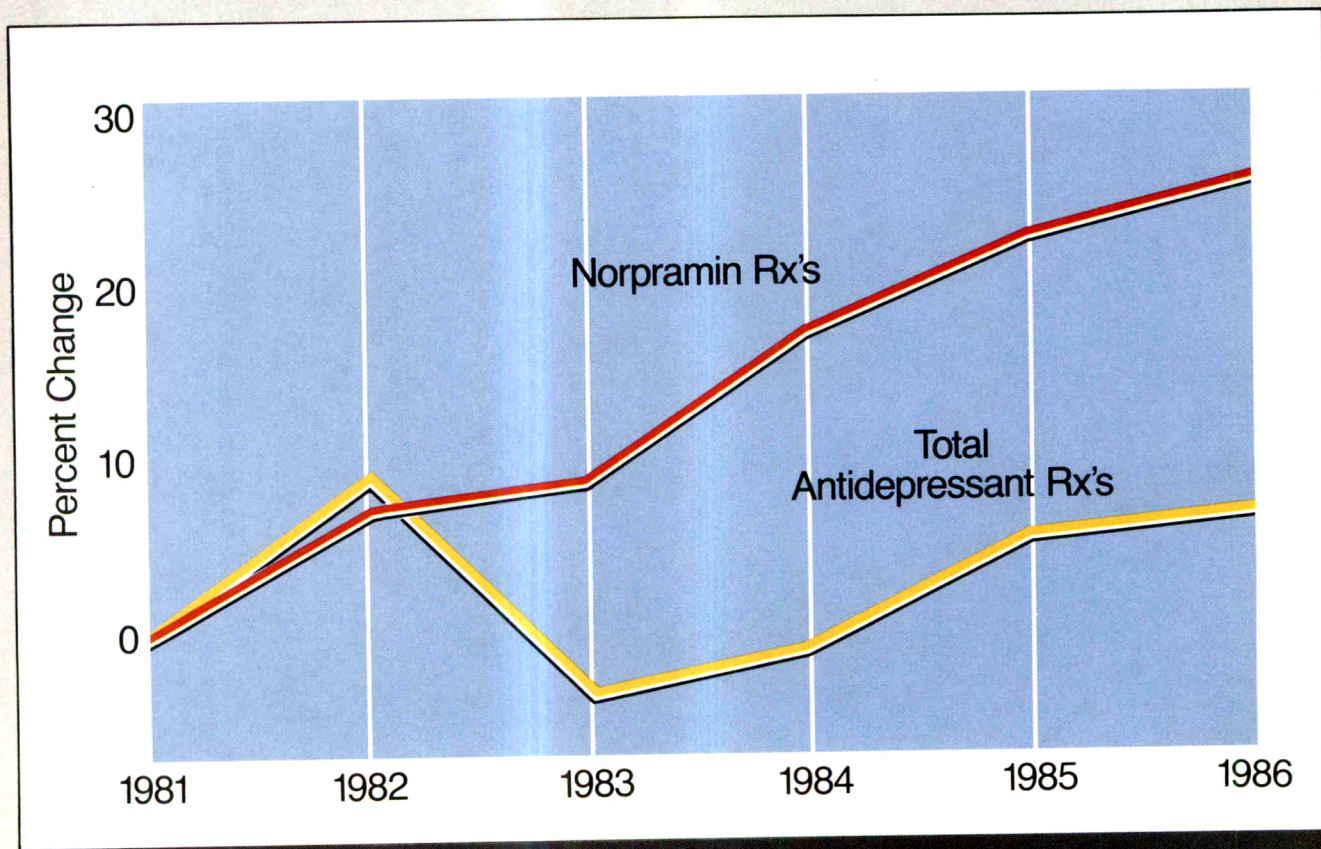


Figure 1.







The red line tracks the percent change in Norpramin prescriptions; the yellow line represents the percent change in total prescription activity in the antidepressant market (based on IMS International *National Prescription Audit*, June 1986).

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Brief Summary

MECHANISM OF ACTION: Available evidence suggests that many depressions have a biochemical basis in the form of a relative deficiency of neurotransmitters such as norepinephrine and serotonin. Norepinephrine deficiency may be associated with relatively low urinary 3-methoxy-4-hydroxyphenyl glycol (MHPG) levels, while serotonin deficiencies may be associated with low spinal fluid levels of 5-hydroxyindolacetic acid.

While the precise mechanism of action of the tricyclic antidepressants is unknown, a leading theory suggests that they restore normal levels of neurotransmitters by blocking the re-uptake of these substances from the synapse in the central nervous system.

Evidence indicates that the secondary amine tricyclic antidepressants, including Norpramin, may have greater activity in blocking the re-uptake of norepinephrine. Tertiary amine tricyclic antidepressants, such as amitriptyline, may have greater effect on serotonin re-uptake.

Norpramin (desipramine hydrochloride) is not a monoamine oxidase (MAO) inhibitor and does not act primarily as a central nervous system stimulant. It has been found in some studies to have a more rapid onset of action than imipramine. Earliest therapeutic effects may occasionally be seen in 2 to 5 days, but full treatment benefit usually requires 2 to 3 weeks to obtain.

INDICATIONS: Norpramin (desipramine hydrochloride) is indicated for relief of symptoms in various depressive syndromes, especially endogenous depression.

CONTRAINDICATIONS: Desipramine hydrochloride should not be given in conjunction with, or within 2 weeks of, treatment with an MAO inhibitor drug; hyperpyretic crises, severe convulsions, and death have occurred in patients taking MAO inhibitors and tricyclic antidepressants. When Norpramin (desipramine hydrochloride) is substituted for an MAO inhibitor, at least 2 weeks should elapse between treatments. Norpramin should then be started cautiously and should be increased gradually.

The drug is contraindicated in the acute recovery period following myocardial infarction. It should not be used in those who have shown prior hypersensitivity to the drug. Cross sensitivity between this and other dibenzazepines is a possibility.

WARNINGS: 1. Extreme caution should be used when this drug is given in the following situations: a. In patients with cardiovascular disease, because of the possibility of conduction defects, arrhythmias, tachycardias, strokes, and acute myocardial infarction. b. In patients with a history of urinary retention or glaucoma, because of the anticholinergic properties of the drug. c. In patients with thyroid disease or those taking thyroid medication, because of the possibility of cardiovascular toxicity, including arrhythmias. d. In patients with a history of seizure disorder, because this drug has been shown to lower the seizure threshold. 2. This drug is capable of blocking the antihypertensive effect of guanethidine and similarly acting compounds. 3. **USE IN PREGNANCY:** Safe use of desipramine hydrochloride during pregnancy and lactation has not been established; therefore, if it is to be given to pregnant patients, nursing mothers, or women of child-bearing potential, the possible benefits must be weighed against the possible hazards to mother and child. Animal reproductive studies have been inconclusive. 4. **USE IN CHILDREN:** Norpramin (desipramine hydrochloride) is not recommended for use in children since safety and effectiveness in the pediatric age group have not been established. 5. The patient should be cautioned that this drug may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. 6. In patients who may use alcohol excessively, it should be borne in mind that the potentiation may increase the danger inherent in any suicide attempt or overdose.

PRECAUTIONS: 1. It is important that this drug be dispensed in the least possible quantities to depressed outpatients, since suicide has been accomplished with this class of drug. Ordinary prudence requires that children not have access to this drug or to potent drugs of any kind; if possible, this drug should be dispensed in containers with child-resistant safety closures. Storage of this drug in the home must be supervised responsibly. 2. If serious adverse effects occur, dosage should be reduced or treatment should be altered. 3. Norpramin (desipramine hydrochloride) therapy in patients with manic-depressive illness may induce a hypomanic state after the depressive phase terminates. 4. The drug may cause exacerbation of psychosis in schizophrenic patients. 5. Close supervision and careful adjustment of dosage are required when this drug is given concomitantly with anticholinergic or sympathomimetic drugs. 6. Patients should be warned that while taking this drug their response to alcoholic beverages may be exaggerated. 7. Clinical experience in the concurrent administration of ECT and antidepressant drugs is limited. Thus, if such treatment is essential, the possibility of increased risk relative to benefits should be considered. 8. If Norpramin (desipramine hydrochloride) is to be combined with other psychotropic agents such as tranquilizers or sedative-hypnotics, careful consideration should be given to the pharmacology of the agents employed since the sedative effects of Norpramin and benzodiazepines (e.g., chlordiazepoxide or diazepam) are additive. Both the sedative and anticholinergic effects of the major tranquilizers are also additive to those of Norpramin. 9. This drug should be discontinued as soon as possible prior to elective surgery because of the possible cardiovascular effects. Hypertensive episodes have been observed during surgery in patients taking desipramine hydrochloride. 10. Both elevation and lowering of blood sugar levels have been reported. 11. Leukocyte and differential counts should be performed in any patient who develops fever and sore throat during therapy; the drug should be discontinued if there is evidence of pathologic neutrophil depression. 12. Norpramin 25, 50, 75, and 100 mg tablets contain FD&C Yellow No. 5 (tartrazine), which may cause allergic-type reactions (including bronchial asthma) in certain susceptible individuals. Although the overall incidence of FD&C Yellow No. 5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity.

ADVERSE REACTIONS: Note: Included in the following listing are a few adverse reactions that have not been reported with this specific drug. However, the pharmacologic similarities among the tricyclic antidepressant drugs require that each of the reactions be considered when Norpramin (desipramine hydrochloride) is given.

Cardiovascular: hypotension, hypertension, tachycardia, palpitation, arrhythmias, heart block, myocardial infarction, stroke. **Psychiatric:** confusional states (especially in the elderly) with hallucinations, disorientation, delusions; anxiety, restlessness, agitation; insomnia and nightmares; hypomania; exacerbation of psychosis.

Neurologic: numbness, tingling, paresthesias of extremities; incoordination, ataxia, tremors; peripheral neuropathy; extrapyramidal symptoms; seizures; alteration in EEG patterns; tinnitus.

Anticholinergic: dry mouth, and rarely associated sublingual adenitis; blurred vision, disturbance of accommodation, mydriasis, increased intraocular pressure; constipation, paralytic ileus; urinary retention, delayed micturition, dilatation of urinary tract.

Allergic: skin rash, petechiae, urticaria, itching, photosensitization (avoid excessive exposure to sunlight), edema (of face and tongue or general), drug fever, cross sensitivity with other tricyclic drugs.

Hematologic: bone marrow depressions including agranulocytosis, eosinophilia, purpura, thrombocytopenia.

Gastrointestinal: anorexia, nausea and vomiting, epigastric distress, peculiar taste, abdominal cramps, diarrhea, stomatitis, black tongue.

Endocrine: gynecomastia in the male, breast enlargement and galactorrhea in the female; increased or decreased libido, impotence, testicular swelling; elevation or depression of blood sugar levels.

Other: jaundice (simulating obstructive), altered liver function; weight gain or loss; perspiration, flushing; urinary frequency, nocturia; parotid swelling; drowsiness, dizziness, weakness and fatigue, headache, alopecia.

Withdrawal Symptoms: Though not indicative of addiction, abrupt cessation of treatment after prolonged therapy may produce nausea, headache, and malaise.

DOSE AND ADMINISTRATION: Not recommended for use in children. Lower dosages are recommended for elderly patients and adolescents. Lower dosages are also recommended for outpatients compared to hospitalized patients, who are closely supervised. Dosage should be initiated at a low level and increased according to clinical response and any evidence of intolerance. Following remission, maintenance medication may be required for a period of time and should be at the lowest dose that will maintain remission.

Usual Adult Dose: The usual adult dose is 100 to 200 mg per day. In more severely ill patients, dosage may be further increased gradually to 300 mg/day if necessary. Dosages above 300 mg/day are not recommended.

Dosage should be initiated at a lower level and increased according to tolerance and clinical response.

Treatment of patients requiring as much as 300 mg should generally be initiated in hospitals, where regular visits by the physician, skilled nursing care, and frequent electrocardiograms (ECG's) are available.

The best available evidence of impending toxicity from very high doses of Norpramin is prolongation of the QRS or QT intervals on the ECG. Prolongation of the PR interval is also significant, but less closely correlated with plasma levels. Clinical symptoms of intolerance, especially drowsiness, dizziness, and postural hypotension, should also alert the physician to the need for reduction in dosage. Plasma desipramine measurement would constitute the optimal guide to dosage monitoring.

Initial therapy may be administered in divided doses or a single daily dose.

Maintenance therapy may be given on a once-daily schedule to patient convenience and compliance.

Adolescent and Geriatric Dose: The usual adolescent and geriatric dose is 25 to 100 mg daily.

Dosage should be initiated at a lower level and increased according to tolerance and clinical response to a usual maximum of 100 mg daily. In more severely ill patients, dosage may be further increased to 150 mg/day. Doses above 150 mg/day are not recommended in these age groups.

Initial therapy may be administered in divided doses or a single daily dose.

Maintenance therapy may be given on a once-daily schedule to patient convenience and compliance.

OVERDOSAGE: See prescribing information for a discussion of symptoms and treatment of overdose.

Product Information as of January, 1985.

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must disclose in their cover letter any commercial or financial involvements that might present an appearance of a conflict of interest in connection with the submitted article, including (but not limited to) institutional or corporate affiliations not already specified in the author's footnote, paid consultancies, stock ownership or other equity interests, and patent ownership. This information will be kept confidential and will not be shared with the reviewers. Such involvements will not be grounds for automatic rejection of the manuscript. Should the article be accepted for publication, the Editor and the authors will consult on whether, and to what extent, this information should be included in the published article.

Patient Anonymity

Ethical as well as legal considerations require careful attention to the protection of a patient's anonymity in case reports and elsewhere. Identifying information such as names, initials, hospital numbers, and dates must be avoided. In addition, authors should disguise identifying information about the characteristics and personal history of patients.

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Manuscripts that report the results of experimental investigation with human subjects must include a statement that informed consent was obtained after the procedure(s) had been fully explained. In the case of children, authors are asked to include information about whether the child's assent was obtained.

Review Process

All papers are reviewed by at least two experts to determine the originality, validity, and importance of content and conclusions. Authors will usually be advised within 3–4 months of the decision on their paper, although delays are sometimes unavoidable. Reviewers' comments will be returned with rejected manuscripts if they are judged to be useful to the authors. All reviewers remain anonymous.

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The original manuscript and three copies should be submitted to John C. Nemiah, M.D., Editor, *American Journal of Psychiatry*, 1400 K St., N.W., Washington, DC 20005. All correspondence will be sent to the first-named author unless otherwise specified. Papers should be accompanied by a cover letter indicating that the paper is intended for publication and specifying for which section of the *Journal* it is being

submitted (i.e., Special Article, Regular Article, Brief Communication, or Clinical and Research Report); they will not be reviewed until such a statement is received.

Authors will be notified of the receipt of their paper and the number assigned to it. **This number must be included in all further correspondence.** It is imperative that the corresponding author of submitted papers notify the *Journal* of changes of address.

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Papers submitted with the request for prompt publication must meet stringent criteria of originality and be of major, immediate importance. Authors must state their reasons for wanting prompt publication in a cover letter to the Editor. These papers are given priority in scheduling; however, authors should be aware that the minimum publication time is 4 months. (This policy is automatic for all Clinical and Research Reports.)

Single Case Reports

Single case reports except for detailed longitudinal studies should be submitted as Letters to the Editor. All single case reports will be peer reviewed. Reports of successfully treated patients should include data on the number of patients treated unsuccessfully by the same method, with an indication of the temporal order of the successes and failures.

Annual Meeting Papers

Authors may submit their papers before the annual meeting, but such papers cannot be published until after the meeting. All papers must be accompanied by a statement that they are in final form. These papers are subject to the same peer review as other papers and must conform to the requirements for one of the types of articles specified in the next section.

TYPES OF ARTICLES

Special Articles

These are usually overview articles that bring together important information on a topic of general interest to psychiatry. Authors who have ideas for such articles are advised to check with the Editor to ensure that a similar work is not in preparation. Special Articles may not exceed 7,500 words (no more than 25 double-spaced pages—including a précis of no more than 100 words, tables, and figures) and may not have more than 100 references.

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The only difference between these two types of papers is length. **Regular Articles** contain no more than 3,800 words, including a précis of no more than 100 words, references, tables, and figures. **Brief Communications** contain no more than 2,500 words, including a précis of no more than 100 words, references, tables, and figures. (A table or figure that fills one-half of a vertical manuscript page equals 100 words of text; one that fills one-half of a horizontal page equals 150 words.) Articles that exceed 3,800 words will be returned unreviewed to the authors.

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A prompt publication policy (i.e., publication within 4 to 6 months after acceptance) is in effect for Clinical and Research Reports. Manuscripts may contain no more than one table and a maximum of 10 references; figures may not be used. Papers may contain a maximum of 1,300 words, including a précis of no more than 40 words, text, references, and an optional table (estimate 15 words per reference, 100 words for a double-spaced table that fills one-half of a vertical page, and 150 words for a double-spaced table that fills one-half of a horizontal page). These articles present 1) new research findings, 2) data from pilot studies, 3) worthwhile replication studies, and 4) clinical studies involving a number of patients. Essays, program descriptions, literature reviews, and single case reports do not meet the criteria for this section. Submissions that exceed 1,300 words or contain figures will be returned to the author.

Other Sections

Letters to the Editor. Brief letters (maximum of 500 words and 5 references; no tables or figures) will be considered if they include the notation "for publication." The number of words should appear in the upper right corner. Letters critical of an article published in the *Journal* will automatically be sent to the authors for reply. Because of space limitations not all letters can be printed. The *Journal* will notify authors about the disposition of their letters but does not return those that are not published. A letter must be signed by all of its authors. All letters will be edited; edited letters will not be sent to authors for approval. Letters must be typed double-spaced throughout on 8½×11 inch paper; two copies are required. Letters that do not meet these specifications will be returned to the author for revision. Reprints of letters are not available. **Single case reports except for detailed longitudinal studies should be submitted as Letters to the Editor. All case reports submitted as Letters to the Editor will be peer reviewed.**

Book Forum. Books for review may be sent to the Book Forum Editor, Nancy C. Andreasen, M.D., Ph.D., University of Iowa College of Medicine, 500 Newton Rd., Iowa City, IA 52242. Book reviews are usually solicited by the Book Forum Editor. Authors interested in reviewing a particular book should communicate directly with Dr. Andreasen. Reprints of reviews are not available.

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All parts of the manuscript, including case reports, quotations, references, and tables, must be double-spaced throughout. Manuscripts must be typed in upper- and lowercase on one side only of 8½×11 inch nonerasable bond paper. All four margins must be 1½ inches. The manuscript should be arranged in the following order, with each item beginning a new page: 1) title page, 2) précis, 3) text, 4) references, and 5) tables and/or figures. All pages must be numbered.

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The number of words, tables, and figures in the paper and the telephone number of the corresponding author

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The précis, or short abstract, is a single paragraph no longer than 100 words for Special Articles, Regular Articles, and Brief Communications and no longer than 40 words for Clinical and Research Reports. Authors should use the active voice and the third person.

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Authors should use the active voice and first person; headings and subheadings should be inserted at reasonable intervals. Footnotes to text may not be used, and summaries are usually unnecessary.

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1. Stone AA: Mental Health and Law: A System in Transition. Rockville, Md, NIMH, 1975, pp 102-103
2. Glick ID, Hargreaves WA, Druet J, et al: Short versus long hospitalization, a prospective controlled study, VII: two year follow-up results for nonschizophrenics. *Arch Gen Psychiatry* 1977; 34:314-320
3. Rubinow DR, Post RM, Pickar D, et al: Relationship between urinary-free cortisol and CSF opiate binding activity in depressed patients and normal volunteers. *Psychiatry Research* (in press)
4. McNamara JR (ed): Behavioral Approaches to Medicine. New York, Plenum Press, 1979
5. Janowsky DS, Judd LL, Huey L, et al: Effects of naloxone in normal, manic and schizophrenic patients: evidence for alleviation of manic symptoms, in Endorphins in Mental Health

Research. Edited by Usdin E, Bunney WE Jr, Kline NS. New York, Oxford University Press, 1979

6. Smythe GA, Compton PJ, Lazarus L: Serotonergic control of human growth hormone secretion: the actions of L-dopa and 2-bromo- α -ergocryptine. *Excerpta Medica International Congress Series* 1976; 381:222-235

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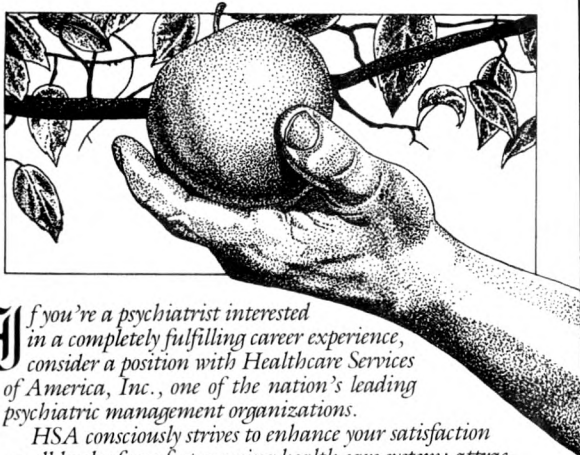
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The Faculty enrolled its first students in 1978 and seeks to educate thoughtful and caring graduates, clinically competent, sensitive and capable with respect to community and psycho-social issues. Its educational programme is community-oriented and based upon problem solving in small group tutorials. There is close integration between disciplines.

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An academic unit has been established at the Newcastle Mater Misericordiae Hospital and liaison services and child psychiatry services will be developed at the New Teaching Hospital, to be opened in 1991.

The Faculty seeks to continue an orientation to preventive care in the community, and community based research.

The Discipline currently consists of the Chair, a Senior Lectureship in Adolescent Psychiatry, a Lectureship/Senior Lectureship (vacant pending appointment to the Chair) and a Professional Officer. It is supported by a substantial number of clinicians in public and private practice. It has an active research programme into adolescent, alcohol and puerperal psychiatric epidemiology, as well as a recognised interest in linguistic and cognitive abnormalities in schizophrenia.

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The University reserves the right to fill the post by invitation.

Further details about this position, the Medical School or its affiliated hospitals, may be obtained from the Dean, Professor J. D. Hamilton, who would welcome enquiries.

Applications close April 10th, 1987.

GENERAL INFORMATION:

Conditions of employment, including method of application and other particulars, may be obtained from the Staff Office, The University of Newcastle, N.S.W., Australia, 2308. Applications (in duplicate) should be addressed to this Unit.

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Applicants must possess a license to practice medicine in Pennsylvania and be board certified in child psychiatry. An active affiliation with an academic program in psychiatry and a demonstrated ability to coordinate research programs is also preferred. A minimum of four years of clinical experience in child and adolescent psychiatry is required.

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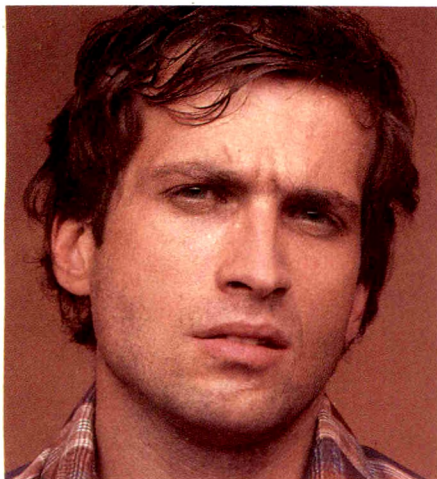
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Contraindications: Since the pharmacologic and clinical actions of HALDOL (haloperidol) Decanoate are attributed to HALDOL as the active medication, Contraindications, Warnings, and additional information are those of HALDOL. Some sections have been modified to reflect the prolonged action of HALDOL Decanoate.

HALDOL is contraindicated in severe toxic central nervous system depression or comatose states from any cause and in individuals who are hypersensitive to this drug or have Parkinson's disease.

Warnings: *Tardive Dyskinesia:* Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown. Both the risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown. Given these considerations, antipsychotic drugs should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that 1) is known to respond to antipsychotic drugs, and 2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically. If signs and symptoms of tardive dyskinesia appear in a patient on antipsychotics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome. For further information about the description of tardive dyskinesia and its clinical detection, please refer to ADVERSE REACTIONS.

Usage in Pregnancy: (see PRECAUTIONS - Usage in Pregnancy) **Combined Use With Lithium:** (see PRECAUTIONS - Drug Interactions).

General: Bronchopneumonia, sometimes fatal, has followed use of antipsychotic drugs, including haloperidol. Prompt remedial therapy should be instituted if dehydration, hemoconcentration or reduced pulmonary ventilation occur, especially in the elderly. Decreased serum cholesterol and/or cutaneous and ocular changes have been reported with chemically-related drugs, although not with haloperidol. See PRECAUTIONS - Information for Patients for information on mental and/or physical abilities and on concomitant use with other substances.

Precautions: Administer cautiously to patients: (1) with severe cardiovascular disorders, due to the possibility of transient hypotension and/or precipitation of anginal pain (if a vasopressor is required, epinephrine should not be used since HALDOL may block its vasopressor activity and paradoxical further lowering of blood pressure may occur; metaraminol, phenylephrine or norepinephrine should be used); (2) receiving anticonvulsant medications, with a history of seizures, or with EEG abnormalities, because HALDOL may lower the convulsive threshold. If indicated, adequate anticonvulsant therapy should be concomitantly maintained; (3) with known allergies or a history of allergic reactions to drugs; (4) receiving anticoagulants, since an isolated instance of interference occurred with the effects of one anticoagulant (phenindione). Concomitant antiparkinson medication, if required, may have to be continued after HALDOL is discontinued because of different excretion rates; if both are discontinued simultaneously, extrapyramidal symptoms may occur. Intraocular pressure may increase when anticholinergic drugs, including antiparkinson drugs, are administered concomitantly with HALDOL. When HALDOL is used for mania in bipolar disorders, there may be a rapid mood swing to depression. Severe neurotoxicity may occur in patients with thyrotoxicosis receiving antipsychotic medication, including HALDOL. The 1, 5 and 10 mg HALDOL tablets contain FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible individuals, especially in those who have aspirin hypersensitivity.

Information for Patients: Mental and/or physical abilities required for hazardous tasks or driving may be impaired. Alcohol should be avoided due to possible additive effects and hypotension.

Drug Interactions: Patients receiving lithium plus haloperidol should be monitored closely for early evidence of neurological toxicity and treatment discontinued promptly if such signs appear.

Carcinogenesis, Mutagenesis and Impairment of Fertility: No mutagenic potential of haloperidol decanoate was found in the Ames Salmonella microsomal activation assay.

Carcinogenicity studies using oral haloperidol were conducted in Wistar rats (dosed at up to 5 mg/kg daily for 24 months) and in Albino Swiss mice (dosed at up to 5 mg/kg daily for 18 months). In the rat study survival was less than optimal in all dose groups, reducing the number of rats at risk for developing tumors. However, although a relatively greater number of rats survived to the end of the study in high dose male and female groups, these animals did not have a greater incidence of tumors than control animals. Therefore, although not optimal, this study does suggest the absence of a haloperidol related increase in the incidence of neoplasia in rats at doses up to 20 times the usual daily human dose for chronic or resistant patients. In female mice at 5 and 20 times the highest initial daily dose for chronic or resistant patients, there was a statistically significant increase in mammary gland neoplasia and total tumor incidence; at 20 times the same daily dose there was a statistically significant increase in pituitary gland neoplasia. In male mice, no statistically significant differences in incidences of total tumors or specific tumor types were noted.

Antipsychotic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and

impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of antipsychotic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time.

Usage in Pregnancy: Pregnancy Category C. Safe use in pregnancy or in women likely to become pregnant has not been established; use only if benefit clearly justifies potential hazards to the fetus.

Nursing Mothers: Infants should not be nursed during drug treatment.

Pediatric Use: Controlled trials to establish the safety and effectiveness of intramuscular administration in children have not been conducted.

Adverse Reactions: Adverse reactions following the administration of HALDOL (haloperidol) Decanoate are those of HALDOL. Since vast experience has accumulated with HALDOL, the adverse reactions are reported for that compound as well as for HALDOL Decanoate. As with all injectable medications, local tissue reactions have been reported with HALDOL Decanoate.

CNS Effects: Extrapyramidal Reactions: Neuromuscular (extrapyramidal) reactions have been reported frequently, often during the first few days of treatment. Generally they involved Parkinson-like symptoms which when first observed were usually mild to moderately severe and usually reversible. Other types of neuromuscular reactions (motor restlessness, dystonia and tardive dyskinesia, akathisia, hyperreflexia, opisthotonos, oculogyric crises) have been reported far less frequently, but were often more severe. Severe extrapyramidal reactions have been reported at relatively low doses. Generally, extrapyramidal symptoms are dose-related since they occur at relatively high doses and disappear or become less severe when the dose is reduced. Antiparkinson drugs may be required. Persistent extrapyramidal reactions have been reported and the drug may have to be discontinued in such cases. **Withdrawal Emergent Neurological Signs:** Abrupt discontinuation of short-term antipsychotic therapy is generally uneventful. However, some patients on maintenance treatment experience transient dyskinetic signs after abrupt withdrawal. In certain cases these are indistinguishable from "Tardive Dyskinesia" except for duration. It is unknown whether gradual withdrawal will reduce the occurrence of these signs, but until further evidence is available HALDOL should be gradually withdrawn. **Tardive Dyskinesia:** As with all antipsychotic agents HALDOL has been associated with persistent dyskinesias. Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may appear in some patients on long-term therapy or may occur after drug therapy has been discontinued. The risk appears to be greater in elderly patients on high-dose therapy, especially females. The symptoms are persistent and in some patients appear irreversible. The syndrome is characterized by rhythmic involuntary movements of tongue, face, mouth or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities and the trunk. There is no known effective treatment for tardive dyskinesia; antiparkinson agents usually do not alleviate the symptoms of this syndrome. It is suggested that all antipsychotic agents be discontinued if these symptoms appear. Should it be necessary to reinstitute treatment, or increase the dosage of the agent, or switch to a different antipsychotic agent, this syndrome may be masked. It has been reported that fine vermicular movement of the tongue may be an early sign of tardive dyskinesia and if the medication is stopped at that time the syndrome may not develop. **Other CNS Effects:**—Insomnia, restlessness, anxiety, euphoria, agitation, drowsiness, depression, lethargy, headache, confusion, vertigo, grand mal seizures, and exacerbation of psychotic symptoms including hallucinations, and catatonic-like behavioral states which may be responsive to drug withdrawal and/or treatment with anticholinergic drugs.

Body as a Whole: Neuroleptic Malignant Syndrome: As with other antipsychotic drugs, a symptom complex sometimes referred to as neuroleptic malignant syndrome (NMS) has been reported. Cardinal features of NMS are hyperpyrexia, muscle rigidity, altered mental status (including catatonic signs), and evidence of autonomic instability (irregular pulse or blood pressure). Additional signs may include elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. NMS is potentially fatal, requires intensive symptomatic treatment and immediate discontinuation of antipsychotic treatment. Hyperpyrexia and heat stroke, not associated with the above symptom complex, have also been reported. **Cardiovascular Effects:** Tachycardia, hypotension, hypertension and ECG changes. **Hematologic Effects:** Reports of mild, usually transient leukopenia and leukocytosis, minimal decreases in red blood cell counts, anemia, or a tendency toward lymphopenocytosis, agranulocytosis rarely reported and only in association with other medication. **Liver Effects:** Impaired liver function and/or jaundice. **Dermatologic Reactions:** Maculopapular and acneiform reactions, isolated cases of photosensitivity, loss of hair. **Endocrine Disorders:** Lactation, breast engorgement, mastalgia, menstrual irregularities, gynecomastia, impotence, increased libido, hyperglycemia, hypoglycemia and hyponatremia. **Gastrointestinal Effects:** Anorexia, constipation, diarrhea, hypersalivation, dyspepsia, nausea and vomiting. **Autonomic Reactions:** Dry mouth, blurred vision, urinary retention, diaphoresis, and priapism. **Respiratory Effects:** Laryngospasm, bronchospasm and increased depth of respiration. **Special Senses:** Cataracts, retinopathy and visual disturbances. **Other:** Cases of sudden and unexpected death have been reported in association with the administration of HALDOL. The nature of the evidence makes it impossible to determine definitively what role, if any, HALDOL played in the outcome of the reported cases. The possibility that HALDOL caused death cannot, of course, be excluded, but it is to be kept in mind that sudden and unexpected death may occur in psychotic patients when they go untreated or when they are treated with other antipsychotic drugs.

IMPORTANT: Full directions for use should be read before HALDOL or HALDOL Decanoate is administered or prescribed. For information on symptoms and treatment of overdose, see full prescribing information.

The short-acting HALDOL injectable form is intended only for acutely agitated psychotic patients with moderately severe to very severe symptoms.

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11/10/86

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Most patients with psychotic symptoms need a quiet, undemanding life that provides refuge from a confusing and overwhelming world.*

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by making sure your patients receive the
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*Emphasis added.

1. Grinspoon L (ed): Care and treatment of schizophrenia—Part II, in *The Harvard Medical School Mental Health Letter* 1986; 3(1): 1.

Patient portrayed by professional model.

Please see brief summary of Prescribing Information on the preceding page.

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